AD

FIFTH INTERNATIONAL CONFERENCE ON HYPERTONIC RESUSCITATION

SYMPOSIUM PROCEEDINGS

GEORGE C. KRAMER

AUGUST 1, 1992

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

Grant No. DAMD17-92-J-2021

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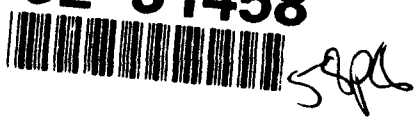

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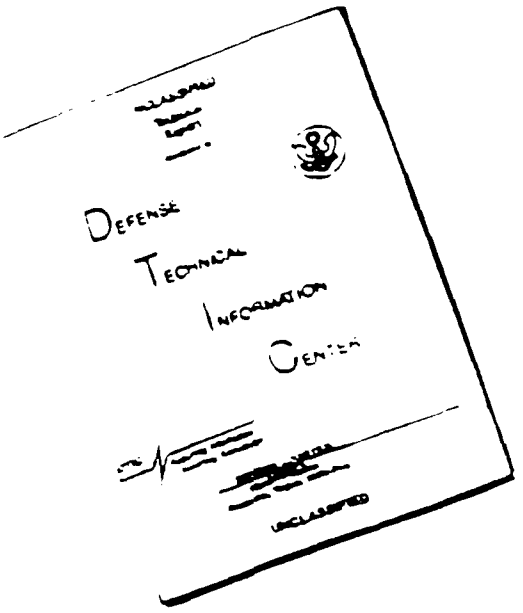

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1, 1992	Symposium Proceedings 3-5 Jun 92

4. TITLE AND SUBTITLE
Fifth International Conference on Hypertonic Resuscitation

5. FUNDING NUMBERS
DAMD17-92-J-2021

6. AUTHOR(S)
George C. Kramer

Bostian

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Texas Medical Branch
503 Clinical Sciences Bldg, G49
Galveston, Texas 77550

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research & Development Command
Fort Detrick
Frederick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release;
distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified		

SALT 5

GALVESTON, JUNE 3-5, 1992

TABLE OF CONTENTS

OVERVIEW

The Fifth International Conference on Hypertonic Resuscitation, "SALT 5," was held at the Tremont House, Galveston, Texas from June 3 to June 5, 1992. This meeting and the previous hypertonic saline conferences are informally called SALT meetings.

There were 85 participants from twelve countries. This included 69 clinicians and scientists active in hypertonic resuscitation as well as 8 representatives from different pharmaceutical companies. Additionally, there were 5 invited speakers and discussants. The FDA was represented and there were 3 representatives from NATO. Two special sessions were held. One was New Approaches to Combat Casualty Care chaired by Major Steve Bruttig. Drs. Robert Mosebar from Fort Sam Houston and Michael Dubick from Letterman Army Institute of Research represented the U.S. Army and Colonel M. Krausz of the Israeli Defense Forces presented another view of combat casualty care. The other was Clinical Trial Design chaired by Charles E. Wade, Ph.D. It included Dr. Curtis Scribner of the FDA, DR. Paul Pepe, a Principal Investigator of the multi-center HSD trials and Dr. Nick Fotheringham, the statistician for the multi-center trials.

A total of 41 abstracts of original research were presented either as ten-minute talks or as posters.

Levels of collegiality and enthusiasm were very high despite the keen debate and scientific repartee that are now traditional with the SALT meetings. Interest and momentum for clinical use continues to grow as several potential new indications for use were discussed. Besides trauma, these now include heat shock, head injury and endotoxemia. Clearly, work remains to better define the physiology, efficacy and potential complications for these new uses, but many investigators are taking up the work.

Previous SALT meetings have been held at Garmisch -P-, Germany in June 1990 - SALT 4; Ilha Bella, Brazil in June 1988 - SALT 3; Monterey, California in June 1986 - SALT 2 and; San Francisco, California in June 1985 - SALT 1. There is no formal society that sponsors the SALT meetings. Rather, a researcher is chosen to organize a meeting and to seek sponsorship every two years. The next SALT meeting will be in Europe in 1994, with Dr. Michael Krausz as it's organizer.

The organizers and participants of the Fifth International Conference on Hypertonic Resuscitation gratefully acknowledge support from:

U.S. Army - Military Research and Development Command

Baxter Healthcare Corp. - IV Systems

Trauma Products, Inc.

Foundation for Advancements in Surgery and Medicine

UTMB Department of Anesthesiology

S A L T 5

Galveston

PROGRAM

Wednesday June 3

1300-1800 **Registration - Lobby**

1800-2000 **Reception - The Rooftop Bar**

Thursday June 4

0800-0830 **Continental Breakfast - Sam Houston Room**

0830-0845 **WELCOME - C. Wade and G. Kramer**

0845-0945 ***Hypertonic Resuscitation and the Brain***
Chairs - D. DeWitt and W. Kröll

S. Berger (Munich, Germany): Therapy of Post-Traumatic Intracranial Hypertension: Mannitol vs. Hypertonic/Hyperoncotic Saline/Dextran

R. Hartl (Munich, Germany): Hypertonic/Hyperoncotic Solutions in Traumatic Brain Injury with Acute Intracranial Hypertension in Rabbits.

L. McDaniel (Galveston, U.S.A.): Effects of Hypertonic Saline Dextran on Intracranial Pressure and Brain Water during Cardiopulmonary Bypass.

U. Strecker (Mainz, Germany): Effect of Hypertonic-Hyperoncotic HES on Recirculation after Global Cerebral Ischemia.

0945-1030 *Hypertonic Saline and the Ischemic Gut*

Chairs - S. Zeigler and D. Traber

L. Frey (Munich, Germany): Hypertonic-Hyperoncotic Saline Dextran (HHS: 7.2% NaCl/10% Dextran 60) Instantaneously Restores Gut Mucosal Blood Flow (BF).

K. Kesel (Munich, Germany): Hypertonic-Hyperoncotic Resuscitation from Hemorrhagic Shock Effectively Improves Intramucosal Acidosis.

C. Cox (Galveston, U.S.A.): Hypertonic Saline-Dextran Does Not Improve Regional Gut Perfusion in a Porcine Model of Pediatric Cardiopulmonary Bypass.

1030-1045 COFFEE BREAK

1045-1215 *Hypertonicity and the Heart*

Chairs - J. Horton and N. Kien

J. Horton (Dallas, U.S.A.): Cardiac Effects of HSD.

J. Kaszaki (Szeged, Hungary): Histamine Release and Cardiac Contractility Changes following Hypertonic Saline Infusion.

S. Mouren (Paris, France): Effects of Hypertonic Saline on Coronary Blood Flow and Myocardial Performance of a Blood-Perfused Isolated Rabbit Heart.

L. Waagstein (Gotëborg, Sweden): Hypertonic Saline for Reversal of Ischemia-Induced Cardiac Dysfunction in the Isolated Rat Heart.

B. Mathew (Galveston, U.S.A.): Comparison of Different Hypertonic Formulations on the Contractility of Isolated Myocardium.

1230-1400 LUNCH AND PANEL DISCUSSION on

New Approaches to Combat Casualty Care

Speakers: Major Steve Bruttig, MSC, Research Physiologist, Letterman Army Institute of Research

Michael M. Krausz, M.D., Professor of Surgery, Hadassah Medical Organization

Michael A. Dubick, Ph.D., Senior Research Pharmacologist, Letterman Army Institute of Research

Dr. Robert Mosebar, Medical Officer, Directorate of Combat and Doctrine Development, Fort Sam Houston

1400-1630 FREE TIME

1530-1630 **Poster Set-up**

1630-1800 **POSTER SESSION 1** - Samuel May Williams Room
Hypertonicity and Organ Systems

A. Cox (Davis, U.S.A.): Effects of Arginine Vasopressin on Urinary Excretion following Administration of 7.5% NaCl/6% Dextran-70.
S. Curtis (Birmingham, U.S.A.): Role of Vasopressin in the Response to Hypertonic Saline in Dextran Following Hemorrhagic Shock.
D. DeWitt (Winston Salem, U.S.A.): Traumatic Brain Injury Impairs Vasodilation to Hemodilution.
C. Doering (Ulm, Germany): Effects of Hypertonic NaCl/Hydroxyethyl-Starch on the Porcine Traumatized Brain in Hemorrhagic Shock.
P. Hellyer (Raleigh, U.S.A.): The Effect of Hypertonic Saline on Myocardial Contractility in Anesthetized Pigs.
H. Ho (Davis, U.S.A.): Effects of Hypertonicity on Hypoxic Rabbit Myocardial Intracellular Sodium and Calcium
J. Iguidbashian (Davis, U.S.A.): Mechanism of the Acute and Infusion-Rate Dependent Hypotension Induced by Hypertonic Saline.
W. Kröll (Graz, Austria): Hypertonic-Hyperoncotic Solutions and Increased Intracranial Pressure (ICP).
H. Ogata (Tochigi Pref., Japan): Efficacies of Hypertonic Saline Solution on the Cardiac Functions and the Plasma Volume during Endotoxic Shock using Dogs.
J. Sondeen (San Francisco, U.S.A.): Resuscitation with 7.5% NaCl/6% Dextran Improves Renal Function in Dehydrated Sheep Following Hemorrhage.
C. Weinstabl (Vienna, Austria): Is a Combination of Hypertonic Saline and Hydroxyethyl Starch (Hyper-HES) a New Concept in Treatment of Raised Intracranial Pressure?

1800-1930 **PANEL DISCUSSION OF DAY'S PRESENTATIONS**
and *Wine and Cheese* - Sam Houston Room
Panel - R. Gunther, N. Kien, D. Traber and W. Kroll

Friday June 5

0800-0830 **Continental Breakfast** - Samuel May Williams Room

0800-0930 **POSTER SESSION**
New Indications and Contraindications of Hypertonic Resuscitation
(Endotoxemia, Dehydration, Uncontrolled Hemorrhage, Acidosis)

M. Dubick (Presidio of San Francisco, U.S.A.): Dextran Metabolism in Dehydrated, Hemorrhaged Sheep Infused with Hypertonic Saline/Dextran (HSD).

J. Eaker (Davis, U.S.A.): Small Volume Intraosseous Resuscitation of Pediatric Hemorrhagic Shock with "Isosal" a New Hypertonic Solution.
L. Figueiredo (São Paulo, Brazil): Hypertonic Solutions following Aortic Occlusion in the Treatment of Uncontrolled Hemorrhagic Shock.
H. Ho (Davis, U.S.A.): 7.5% Sodium Chloride-6% Dextran-70 Fluid Resuscitation of Hemorrhagic Dehydrated Sheep.
C. Matthew (Natick, U.S.A.): Treatment of Hyperthermia and Dehydration with Hypertonic Saline in Dextran (HSD).
Jörg Meyer (Galveston, U.S.A.): Continuous Small Volume Resuscitation with Hypertonic Saline Dextran Solution Improves Survival in Experimental Sepsis.
P. Moon (Galveston, U.S.A.): Comparison of Resultant Acid-Base Balance after Small Volume Resuscitation with Hypertonic Saline/Dextran or Hypertonic Acetate/Dextran.
D. Nolte (Munich, Germany): Evidence for Altered Expression of the L-selectin (LECAM-1) on Human Blood PMNs by Hypertonic Saline.
M. Rocha e Silva (São Paulo, Brazil): Isochloremic and Isonatremic Formulations for Hypertonic Resuscitation from Severe Uninterrupted Blood Loss in Dogs.

0930-1030 SLIDES - Sam Houston Room
Chair - R. Gunther

G.I. Elgjo (Kjeller, Norway): The Role of Adrenaline in Cardiovascular Responses to Hypertonic Saline in Hemorrhaged Conscious Rats.
M. Krausz (Jerusalem, Israel): The Effect of Heating on Hypertonic Saline Treatment of Uncontrolled Hemorrhagic Shock (UCHS).
M. Rocha e Silva (São Paulo, Brazil): Pressure Driven Hemorrhage as a Simulation of Uncontrolled Arterial Hemorrhage: An Experimental Study in Dogs.
U. Strecker (Mainz, Germany): The Effect of the Type of Colloid on the Efficacy of Hypertonic NaCl Colloid Mixtures in Hemorrhagic Shock Dextran vs. HES.

1030-1045 COFFEE BREAK

1045-1130 PANEL DISCUSSION OF MORNING PRESENTATIONS
Panel - M. Rocha e Silva and K. Messmer

1130-1330 LUNCH - FREE TIME

1330-1430 *Clinical Trial Design* - Sam Houston Room

Chair - Charles E. Wade, Ph.D., Deputy Chief, Life Sciences Division, NASA

Speakers - Paul E. Pepe, M.D.; Director, City of Houston Center for Resuscitation and Emergency Medical Services
Nick Fotheringham, Ph.D., Dixon Statistical Associates
Curtis L. Scribner, M.D., Chief, Hematologic Products Branch, FDA

1430-1630 *Current Clinical Uses of Hypertonic Solutions*

Chairs - M. Krausz and C. Scribner

A. Chávez-Negrete (Mexico City, Mexico): Effectiveness of Hypertonic/ Hyperosmotic Solutions in Decreasing CPK Enzymatic Output during Reperfusion after Thrombolysis in Myocardial Infarction.

P. Pepe (Houston, U.S.A.): Deliberate Fluid Restriction in Post Traumatic Hypovolemic Hypotension.

L. Frey (Munich, Germany): Hypertonic-Hyperoncotic Saline Dextran (HHS:7.2% NaCl/10%DX60) in Septic Shock-Preliminary Results of an Ongoing Clinical Trial.

S. Majluf (Mexico City, Mexico): Evaluation of an Intraosseous Function versus Intravenous and Central Catheter in Patients with Hemorrhagic Shock.

W. Schaffartzik (Berlin, Germany): Hypertonic Saline Solution and Pulmonary Gas Exchange.

R. Younes (São Paulo, Brazil): Hypertonic Saline-Dextran in the Treatment of Hemorrhagic Shock: Clinical Trial in the Emergency Room.

1630-1730 **CONCLUDING PANEL DISCUSSIONS**

2000-2130 **BANQUET:** ***Cody's on the Strand***
2215 Strand

ABSTRACTS

(alphabetically arranged by first author)

THERAPY OF POST-TRAUMATIC INTRACRANIAL HYPERTENSION: MANNITOL VS. HYPERTONIC/HYPERONCOTIC SALINE/DEXTRAN

Steffen Berger, Ludwig Schürer[1], Roger Härtl, Konrad Messmer, Alexander Baethmann

Institute for Surgical Research and Department of Neurosurgery[1], Klinikum Großhadern, Ludwig-Maximilians-University, Marchioninistr. 15, 8000 Munich 70, F.R.G.

Background: Small-volume resuscitation in hemorrhagic shock by hypertonic/hyperoncotic solutions (HHS), e.g. 7.2 % NaCl and 10 % Dextran 60 is currently under clinical investigation. Since up to 30 % of cases with polytrauma are simultaneously affected by severe head injury, the treatment might be employed also in this group of patients. Yet, effects of HHS on damaged brain tissue are largely unknown so far. Our laboratory has demonstrated a reduction of the intracranial pressure (ICP) by HHS in acute experimental brain damage (cf. Abstract: Härtl et al.). Since these results indicate effectiveness of HHS in intracranial hypertension in patients with head injury and shock, respective studies were continued now in order to compare the therapeutical potential of HHS with that of mannitol. For that purpose HHS or mannitol, respectively were administered 24 hrs after experimental head injury at a time period when brain edema is maximally developed.
Methods: New Zealand albino rabbits (n=12) were anesthetized by ketamine/xylazine. A focal cold injury of the exposed brain surface was induced after osteoclastic trephination of the skull, leaving the dura intact. An epidural balloon was inserted in addition between the traumatized brain parenchyma and the skull bone followed by closure of the cranium by dental cement. At 20 hrs later the animals were reanesthetized by α-chloralose and implanted with arterial and venous catheters, tracheotomized, and artificially ventilated. Arterial blood pressure (MAP), blood gases, Hct, and body temperature were monitored continuously or at intervals. The ICP was raised to 17 mmHg by inflation of the balloon. After a control period of 30 min either HHS (4 ml/kg b.w.) or 20 % mannitol (9 ml/kg b.w.) were i.v. infused within two minutes at 24 hrs after induction of the brain lesion. The osmotic load administered in both groups was equivalent amounting to 9.6 mosmol/kg b.w..
Results: Initially ICP, MAP and other physiologic parameters were not different between the experimental groups. MAP, colloid-osmotic pressure, and the Na^+ -concentration in plasma had a tendency to increase after HHS, while to decrease after mannitol. Plasma osmolarity was increased by 15-20 mosmol/l at 10 min after administration of either solution, but was found to normalize thereafter. ICP was lowered for 98 min by HHS, for 189 min by mannitol. When administration of each regimen was repeated, ICP was lowered for 142 min by HHS, while for 106 min by mannitol. In two animals with mannitol, one with HHS, the ICP remained decreased for more than 4 hrs, making unnecessary subsequent administration of the hypertonic solutions. In both groups, with either HHS or mannitol the ICP minimum at 4-6.5 mmHg was obtained at 20 min after start of the infusion.
Conclusions: As shown, intracranial hypertension can be therapeutically influenced by either HHS or mannitol with equivalent efficiency. However the plasma- osmolarity and -Na^+ concentration were more increased by HHS. Nevertheless, the present findings suggest that HHS is beneficial not only for the treatment of circulatory failure in polytraumatized patients with hemorrhagic shock, but also as primary care in cases with additional head injury.

EFFECTIVENESS OF HYPERTONIC/HYPEROSMOTIC SOLUTIONS IN DECREASING CPK ENZYMATIC OUTPUT DURING REPERFUSION AFTER THROMBOLYSIS IN MYOCARDIAL INFARCTION

Adolfo Chávez-Negrete, Pilar Suare., Ricardo Aviles and Rubén Argüero

Department of Internal Medicine, Division of Emergencies and Cardiothoracic Surgery, Hospital de Especialidades Centro Médico La Raza, IMSS, México, D.F., México

Background:

Post-ischemic reperfusion causes microcirculatory dysfunctions including endothelial edema, leukocyte activation and adhesion, and the generation of oxygen free radicals. The treatment of acute myocardial infarction (AMI) often causes reperfusion injury on and beyond the evident benefits of thrombolysis, bypass surgery and angioplasty. To the present there is no clinical/pharmacological method that protects the tissue at risk from reperfusion injury. Our objective was to demonstrate the efficacy of the hypertonic/hyperosmotic solution (7.5% NaCl, 6% Dextran 60 (H/H) in decreasing the concentration of creatinphosphokinase after thrombolysis in AMI.

Methods:

30 patients with AMI were divided at random into three groups: Group I, 10 patients (49 ± 7 y) eligible for thrombolysis with streptokinase (SK, 1.5 x 10^6 units); Group II, 11 patients (53 ± 6 y) receiving 4 ml/kg of H/H prior to the infusion of SK; Group III, 9 patients (58 ± 8 y) who were not eligible for SK. Each group was evaluated each 4 hoursin terms of elevation of CK-MB and ECG, red cell count, fibrinogen and cholesterol, prior to treatment and 36 hours after. Coronary angiography and ecocardiography was used to evaluate vascular damage and ejection fraction.

Results:

There was no difference in the topography of the infarct, nor were there any differences in the age and coronary risk between groups. However, comparison between the CK washout curves between the groups showed a significant difference at 4 and 8 hours after AMI, namely Groups I, II and III at 4 and 8 hours had CK concentrations of 800 and 1395, 367 and 550, 368 and 514 mu/ml respectively ($p < 0.05$). 8/10 of Group I and 2/11 of Group II had different degrees of arrhythmias up to 8 hours after thrombolysis ($p < 0.05$).

Conclusions:

Hypertonic/hyperosmotic solutions avoid the enzymatic increase of CK in the initial phase in the treatment of AMI by thrombolysis and show an improved clinical evolution relative to conventional thrombolysis, suggesting a decreased reperfusion damage.

EFFECTS OF ARGININE VASOPRESSIN ON URINARY EXCRETION FOLLOWING ADMINISTRATION OF 7.5% NACL/6% DEXTRAN-70

Alan T. Cox, Hung S. Ho and Robert A. Gunther

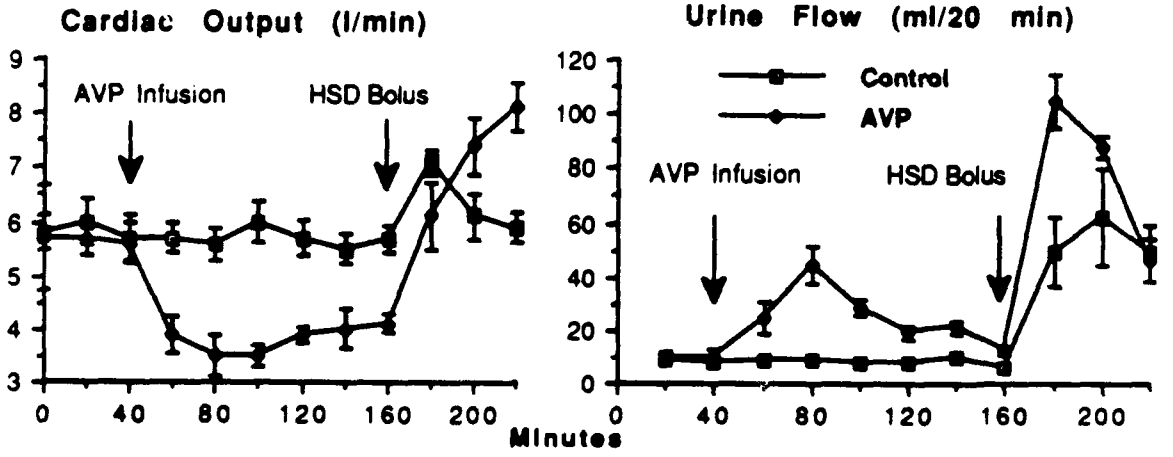
Department of Surgery, University of California Davis, CA 95616

Background: Hypertonic saline/dextran-70 (HSD) solution effectively restores cardiovascular function following severe hemorrhagic shock in animals. However, there is an unexplained diuresis following HSD resuscitation even in the presence of a continued hypovolemic state and high levels of the anti-diuretic hormone, AVP (Surgery 100:239, 1986). On the other hand, studies have shown that excessively elevated AVP levels can cause a diuresis (Nature 192:1084, 1961). Therefore, we conduct this study to test the hypothesis that the marked diuresis following HSD injection may be enhanced by the high plasma AVP levels.

Methods: Adult sheep, 40-45 kg, were surgically implanted with indwelling silastic catheters and a Swan-Ganz thermodilution catheter for monitoring of hemodynamic function. A Foley catheter was used for urine collection on the day of each experiment. Hemodynamic data and urine volumes were measured every 20 minutes throughout the experiment. Baseline values were obtained for 1 hour, followed by a 2-hour IV infusion of either AVP or a control solution (0.9% NaCl). At the end of the infusion period, a HSD bolus (4ml/kg) was administered. Subsequent measurements were taken for 1 hour following the bolus.

Results: mean ± SEM, n = 6 in each group

Parameters	Group	BL/min	AVP/1hr	AVP/2hr	HSD/20min	HSD/60min
MAP	AVP	92 ± 5	100 ± 6	97 ± 4	105 ± 1	101 ± 4
(mmHg)	Control	97 ± 3	102 ± 3	102 ± 2	109 ± 3	97 ± 2
HR	AVP	108 ± 9	68 ± 7	60 ± 4	75 ± 5	102 ± 8
(beats/min)	Control	102 ± 14	108 ± 9	92 ± 7	105 ± 11	86 ± 9



Conclusion: AVP levels in our model induced bradycardia leading to a decreased cardiac output, yet increased urine flow. Following HSD injection, the presence of AVP potentiated the diuretic effects of the HSD. These data suggest that high levels of AVP during hemorrhagic shock may contribute to the diuretic effects seen after HSD resuscitation. Therefore, by reducing plasma AVP, one may be able to prolong the benifcial effects of HSD on the hemodynamics.

HYPERTONIC SALINE-DEXTRAN DOES NOT IMPROVE REGIONAL GUT PERFUSION IN A *PORCINE* MODEL OF CARDIOPULMONARY BYPASS.

Charles S. Cox, Jr., MD, Joseph B. Zwischenberger, MD, R.Y. Declan Fleming, MD, Tamara Myers BS, Mark Kurusz, CCP, David N. Herndon MD, George C. Kramer PhD.

University of Texas Medical Branch and Shriners Burns Institute.

There is indirect evidence of hypoperfusion of the gastric mucosa and the entire gastrointestinal tract during cardiopulmonary bypass (CPB). An ischemic gut may contribute to multiple post-operative complications. Hypertonic saline/dextran (HSD) has been reported to decrease resuscitation fluid requirements, and preferentially augment mesenteric blood flow and microvascular perfusion in models of hypovolemia. Therefore, we studied the effects of adding HSD to the circuit prime solution on volume requirements during CPB, as well as the micro and macrocirculation of the gut, and renal artery blood flow. **METHODS**: Two groups of 3-5 month old *swine* were instrumented with Transonic superior mesenteric (SMA), renal artery (REN), and ileal mucosal (IM) laser Doppler flow probes. All pigs underwent normothermic, noncrossclamped bicaval to aorta CPB for 120 minutes. Group HSD (n=7) received 1 ml/kg of 25% saline/24% dextran added to the standard isotonic prime of 1000 ml plasmalyte/500 ml 6% hetastarch. Group LR (n=8) had a standard prime of plasmalyte/6% hetastarch alone. Pump flow was maintained at 85-100 ml/kg/min, and isotonic volume was added to maintain the oxygenator at constant volume. Regional blood flows and volume requirements were measured every 15 minutes. **RESULTS**: Net fluid balance during CPB was significantly lower in HSD compared to LR (1126±685ml vs. 4509±470ml respectively; $p< 0.05$ unpaired Student's t-test). Renal blood flow was not significantly altered in either group. Gut blood flows are shown in the table below.

Groups	Variable	**Baseline**	**30 MIN**	**60 MIN**	**90 MIN**	**120 MIN**
HSD	**SMA**	444±56	503±74	451±67	374±88	378±73
	IM	19±2	13±3	8±2*	8±2*	6±2*
LR	**SMA**	508±73	745±119	730±96#	787±122 # *	751±93 #
	IM	24±3	9±2*	11±2*	11±1*	11±2*

SMA ml/min; IM in ml/100gm tissue/min; Within group comparisons to baseline by ANOVA and Dunnett's test, * $p< 0.05$; Between group comparisons at individual timepoints with unpaired t-test, # $p< 0.05$.

CONCLUSIONS: These data suggest that the addition of HSD to the circuit prime can lower volume requirements, but does not ameliorate the decrease in ileal mucosal blood flow that occurs during CPB.

ROLE OF VASOPRESSIN IN THE RESPONSE TO HYPERTONIC SALINE IN DEXTRAN FOLLOWING HEMORRHAGIC SHOCK

Scott E. Curtis, Julie T. Peek, Benoit Vallet, Wayne E. Bradley, and Stephen M. Cain.

Dept. of Pediatrics and Physiology and Biophysics, University of Alabama at Birmingham, Birmingham, AL 35294, and the Dept. of Critical Care Medicine, University of Lille, France.

Background: The marked increase in serum arginine vasopressin (AVP) following acute hemorrhage significantly contributes to mean arterial pressure (MAP). Hypertonic (7%) saline in 6% dextran (HSD) given after hemorrhage acutely lowers AVP levels, though they remain significantly above baseline. In this study we used the V_1V_2 blocker O-Et-Tyr,Val,AVP to test the hypothesis that AVP contributes to the complex therapeutic actions of HSD.

Methods: 8 dogs were ventilated with room air following anesthesia and muscle relaxation. Catheters were placed in the pulmonary and carotid arteries for pressure monitoring and blood sampling. The venous outflow of one hindlimb and a segment of ileum were catheterized to permit measurement of regional oxygen delivery (Do_2) and uptake (Vo_2) as previously described (1). Whole body Vo_2 was measured by exhaled gas analysis. After baseline measurements, all dogs were bled to a MAP of 40 torr over 5 min. 30 min later, we gave 5 ml/kg of HSD intravenously over 3 to 5 min, simultaneous with 10 µg/kg of AVP blocker (AVP-bl). Data were collected every 15 min for 2 additional hr. Results were compared to previously studied non-blocked HSD-resuscitated dogs (CON,n=8) (1).

Results: Blood loss, Hct, and osmolality at all time points were similar between AVP blocked and control groups. The whole body and limb Do_2 and Vo_2 response to HSD resuscitation also did not differ significantly between groups. Following resuscitation, systemic vascular resistance and MAP were significantly lower in AVP-bl than in CON. In the gut, resistance was markedly lower, Do_2 and fraction of cardiac output higher, and oxygen extraction ratio lower after resuscitation in AVP-bl than CON, though Vo_2 was similar.

Conclusion: Following an average hemorrhage of 40 ml/kg, 5 ml/kg of HSD was able to restore systemic, skeletal muscle, and gut hemodynamics and O_2 metabolism in both groups. AVP helped maintain MAP and acted to limit gut blood flow after HSD treatment, but blockade of V_1 and V_2 receptors showed that vasopressin activity was not essential for successful resuscitation with HSD.

1. Curtis SE and Cain SM. Am J Phys 262 (Heart, Circ Phys 31): H778, 1992.

Supported by an ALA Trudeau Award to SEC and by NIH grant #HL26927 to SMC.

TRAUMATIC BRAIN INJURY IMPAIRS VASODILATION TO HEMODILUTION

Douglas S. DeWitt, Donald S. Prough, Scott M. Vines, Dwight D. Deal

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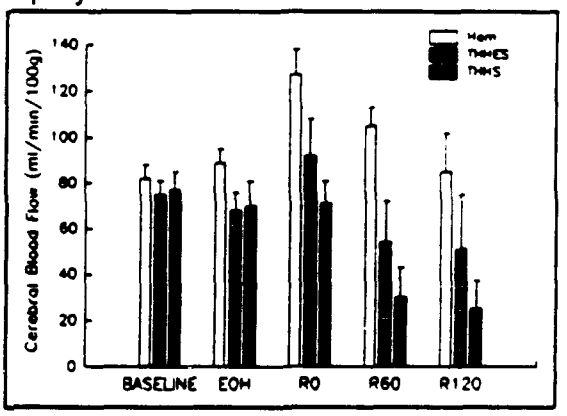
Background: Hemorrhagic hypotension after traumatic brain injury (TBI) in humans is associated with higher mortality and morbidity than TBI alone (1). Crystalloid and colloid solutions have been used to restore systemic hemodynamics and cerebral blood flow (CBF)(2). Isovolemic hemodilution with crystalloid (3) or colloid (4) solutions increases CBF but the effects of these fluids on CBF after TBI remains unknown. To determine whether TBI affects compensatory vasodilation to hemodilution, we measured CBF in cats after TBI, hemorrhagic hypotension and resuscitation with hydroxyethyl starch (HES) or hypertonic saline (HS).

Methods: In an IACUC-approved protocol, cats were anesthetized with ketamine (25mg/kg), intubated, ventilated with 1.6% isoflurane in N_2O:O_2 (70:30) and prepared for TBI and for microsphere CBF measurements. Following surgery, isoflurane concentration was decreased to 0.8% in N_2O. Cats were hemorrhaged (-30% blood volume) and resuscitated with HES (Hem, n=8) or subjected to TBI (2.7 atm), hemorrhaged and resuscitated with 10% HES (THHES, n=8) or with 3.0% saline (THHS, n=8). CBF was determined pre-injury (baseline), after hemorrhage (EOH), and 0, 60 and 120 minutes after resuscitation (R0, R60, R120).

Results: After hemorrhage and resuscitation without TBI, CBF increased above baseline (R0, Figure) and remained above baseline in Group Hem at R60 and R120. In contrast, there was little or no increase in CBF during hemodilution in the groups sustaining TBI. In addition, CBF in the trauma groups fell markedly by R60 and R120 regardless of the resuscitation fluid employed.

Conclusion: Moderate fluid percussion TBI impairs the vasodilatory response to hemodilution. Neither HES nor HS produced prolonged support of CBF following TBI and hemorrhagic hypotension. These data suggest that fluid resuscitation alone may be inadequate to restore CBF following trauma and hemorrhage and that additional pharmacological treatment (i.e. opiate antagonists, 5) may be required.



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EFFECTS OF HYPERTONIC NACL/HYDROXYETHYLSTARCH ON THE PORCINE TRAUMATIZED BRAIN IN HEMORRHAGIC SHOCK

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Background: 'Small volume resuscitation' with hypertonic NaCl-solutions has been proven efficient for the acute treatment of hemorrhagic shock. However, little has been known of the long-term cerebral effects of these solutions in the presence of traumatic head injury (HI).
Methods: We studied 27 swine following fluid percussion HI and 30 minutes of hemorrhagic shock (HS) (mean arterial pressure: 55 mmHg). At this point animals received a bolus (4 ml/kg BW) of either 7.5% NaCl/6% Hydroxyethylstarch (HES) (Group I, n=9) or 6% HES (Group II, n=11). Controls with HS but without HI received a bolus of NaCl/HAES (Group III, n=7). 30 minutes after this initial bolus animals in all groups were infused shed blood to achieve baseline filling pressures. Collected data included cardiac output (CO, l/min), mean arterial pressure (MAP, mmHg) and intracranial pressure (ICP, mmHg). Study period was 8 hours.
Results: Hypertonic NaCl/HES resulted in a transient rise of CO and MAP to subnormal levels lasting for 30 minutes, whereas ICP was reduced to baseline levels for a period of 1 hour. After 8 hours, however, ICP in groups I and III had reached the elevated levels measured in group II 30 minutes after the initial volume therapy. (Data: means $\pm$ SEM; * $p < 0.05$).

		Cardiac Output	ICP
End of Shock Period	Group I	2.7 $\pm$ 0.3	7 $\pm$ 2
	Group II	2.3 $\pm$ 0.2	6 $\pm$ 1
	Group III	2.2 $\pm$ 0.2	6 $\pm$ 1
30 minutes after volume bolus	Group I	3.6 $\pm$ 0.4	7 $\pm$ 2
	Group II	6.6 $\pm$ 0.5 *	13 $\pm$ 1 *
	Group III	3.9 $\pm$ 0.2	5 $\pm$ 1
8 hours after initial bolus	Group I	4.8 $\pm$ 0.4	15 $\pm$ 3
	Group II	3.8 $\pm$ 0.2	18 $\pm$ 4
	Group III	4.4 $\pm$ 0.4	11 $\pm$ 1

Conclusion: Hypertonic NaCl/HES had the same qualitative hemodynamic effect as HES alone. However, hemodynamic improvement with NaCl/HES was less marked and only transient. Additional volume substitution was necessary for the definite therapy of hemorrhagic shock. With NaCl/HES, the hemodynamic improvement was accompanied by a significant reduction of ICP, which was abolished after 8 hours.

DEXTRAN METABOLISM IN DEHYDRATED, HEMORRHAGED SHEEP INFUSED WITH HYPERTONIC SALINE/DEXTRAN (HSD).

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Background: In recent years, concern has been raised whether concomitant dehydration would adversely affect the ability of HSD to effectively resuscitate hemorrhagic hypotension. Of particular concern was an adverse effect on renal function. Since the early phase of dextran clearance is through glomerular filtration and excretion in the urine, the present study examined dextran concentrations and molecular size distribution in urine and plasma to determine if dehydration increased the renal excretion of dextran, and therefore, alter the biological half-life of HSD.

Methods: After a 4 day dehyration period, adult, chronically instrumented ewes (n=6) were bled until mean arterial pressure reached 50 mm Hg. After a 2 hr hypotensive period, animals were infused with 4 ml/kg HSD and blood and urine samples were collected over a 2 hr period, after which time animals were reinfused with their shed blood and allowed free access to food and water. Each animal was followed over the next two weeks. A blood sample was taken daily over the first week and then at 2 wks.

Results: Plasma dextran concentrations peaked in the first 30 to 60 min after HSD infusion at 454$\pm$42 mg/dl. Preliminary estimates of plasma dextran clearance indicated a half-life of 13.0$\pm$1.7 hr. In urine, dextran excretion appeared to be a function of both renal plasma flow and urine volume, i.e., parameters dependent on adequate resuscitation following HSD infusion. As a result of initial analysis in 4 ewes, dextran excretion in urine, as a percentage of the dose infused varied from 7-27%. Evaluation of the molecular size distribution of dextran in urine, from 30 to 120 min after HSD infusion, showed a peak molecular weight of 40,000 or less. No significant 70,000 molecular weight fractions were observed in urine, whereas this was the predominant molecular weight distribution in plasma.

Conclusion: Dextran metabolism in dehydrated sheep followed typical patterns observed in previous studies with euhydrated animals. The lack of 70,000 molecular weight components of dextran in urine suggest an intact renal glomerulus and support other data that renal function is not compromised by HSD in hemorrhaged, dehydrated sheep. Consequently, dehydration should not affect the early phase of plasma dextran clearance and its half-life.

SMALL VOLUME INTRAOSSEOUS RESUSCITATION OF PEDIATRIC HEMORRHAGIC SHOCK WITH "ISOSAL" A NEW HYPERTONIC SOLUTION.

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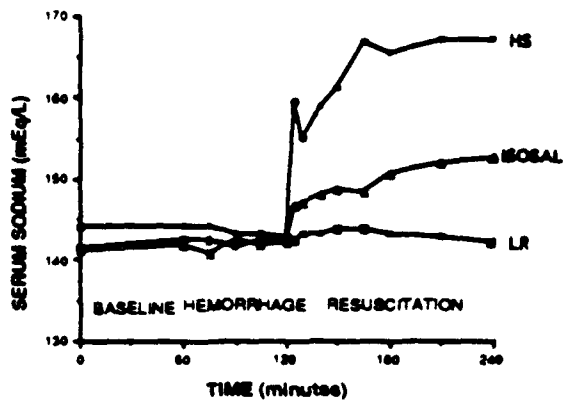
BACKGROUND: In severe hypovolemic shock it is impractical to administer large volumes of fluid quickly through the intraosseous (I/O) route. We have developed a pediatric animal model of severe hemorrhagic shock to compare conventional isotonic fluids to hypertonic "small volume" fluids through the I/O route. Hypertonic saline (HTS) is effective in small volumes, but hypernatremia limits the volume that can be safely used. A new hypertonic solution (Isosal) consisting of saline, glucose, and amino acids was formulated to provide the same beneficial cardiovascular effects of HTS without the side effect of increased serum sodium.

METHODS: Seventeen piglets (mean weight 10 Kg) were anesthetized with Isoflurane and instrumented with a pulmonary artery catheter, arterial and venous catheters, and an intraosseous device. Severe hemorrhagic shock was achieved by bleeding the animals to a cardiac output (CO) of 50% baseline value for 1 hour and, resuscitation was carried out through the I/O route using either Lactated Ringers (LR), 7.5% Hypertonic Saline (HTS), or Isosal (ISO), to maintain baseline CO for 2 hours.

RESULTS:

Fluid	n	Bled Vol. (ml/kg)	Resus vol. (ml/kg)
LR	6	45.5 + 4.1	75.3 +11.6
HTS	5	37.4 + 3.5	12.7 + 1.2
ISO	6	44.5 + 4.0	12.5 + 4.1

Resuscitation with hypertonic fluids required 85% less volume ($p<0.05$); HTS and Isosal were equally effective in restoring and maintaining CO.



Serum sodium was significantly higher with HTS when compared to either LR or ISO ($p<0.05$).

CONCLUSION: In severe pediatric hemorrhagic shock I/O resuscitation with "small volume" hypertonic fluids is effective. Hypernatremia seen with HTS is not a significant problem with Isosal - a new "isonatremic" hypertonic solution".

THE ROLE OF ADRENALINE IN CARDIOVASCULAR RESPONSES TO HYPERTONIC SALINE IN HEMORRHAGED CONSCIOUS RATS

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The purpose of this study was to determine if adrenaline plays a role in the hemodynamic responses to hypertonic saline (HTS 8.0 mg/ml) in male Wistar Kyoto rats. Several findings suggest that adrenaline may contribute to hemodynamic responses to hypotension and to HTS: Both hypotension, and HTS given i.c.v., produce a substantial increase in adrenal sympathetic nervous activity (1). Differential control of adrenal and renal sympathetic nerve activity during hypotensive hemorrhage has been demonstrated in rats (2). HTS enhances the spontaneous release of catecholamines in cat adrenal glands in vitro (3).
Animals were subjected to adrenal demedullation (ADMX, n=14) or sham operation (SHAM, n=10). Indwelling catheters were placed in a.fem.sin. and v.jug.ext. After 7-9 days, mean arterial pressure (MAP) and heart rate (HR) were recorded in conscious, freely moving animals. Blood was withdrawn through the venous catheter and MAP kept at 50 mmHg for one hour. Arterial blood samples (0.55 ml) were taken for analysis of catecholamines and hematocrit (HCT). After 1 h hypotension, HTS i.v. (2.0 ml/kg, 0.4 ml/min) produced an immediate increase in MAP and HR in both groups.
Results: mean(range)

	pre-hemorr.	hypotens.	HTS + 10min	HTS + 120min
SHAM MAP	107(89-121)	49(43-52)	116(96-124)	85(50-112)
ADMX MAP	97(85-112)	48(44-53)	109(92-120)	84(40-106)
SHAM HR	359(284-436)	(~100-300)	378(266-444)	365(236-600)
ADMX HR	374(320-443)	(~100-300)	365(234-470)	337(270-444)
SHAM HCT	45(42-49)	37(33-40)	36(33-40)	32(28-35)
ADMX HCT	41(38-44)	34(31-37)	34(32-37)	32(28-38)

Within 10 min after HTS, HR and MAP in both groups increased more than 100%. Between 10 and 120 min after HTS, HCT fell by 13% in the SHAM group as compared to 6% in the ADMX group. 24 hours after HTS, MAP and HR in both groups had normalised. In conclusion, the hemodynamic responses were similar in the two groups, suggesting that hormonal factors released from the adrenal medulla do not play a major role in the response to HTS (2.0 ml/kg) in the rat.

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HYPERTONIC SOLUTIONS FOLLOWING AORTIC OCCLUSION IN THE TREATMENT OF UNCONTROLLED HEMORRHAGIC SHOCK.

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Background and methods: The use of hypertonic solutions as the initial treatment of uncontrolled hemorrhagic shock from abdominal source is controversial. The present study evaluates the hemodynamic effects of transfemoral aortic occlusion (**AO**) with balloon catheter followed by hypertonic solutions in 28 pentobarbital anesthesied dogs submitted to uncontrolled pressure driven hemorrhage during 90 min (initial bleeding rate: 25 ml/Kg; thereafter, proportional to **MAP** in abdominal aorta). Dogs were randomized into 4 groups, according to the treatment employed in min 34, bolus injection=4 ml/k: **NS**: no occlusion, **NaCl**: 0,9%,; **AO-NS**:NaCl 0,9%; **AO+HS**:NaCl 7,5%, 2400 mOsmol/l; **AO+HA**:sodium acetate,10.5%, 2400 mOsmol/l.

Results: The table displays values for mean arterial pressure, systemic vascular resistance index, cardiac index, stroke index, mean pulmonary arterial pressure, wedge pressure hematocrit and cumulative blood loss. Treatment at asterisk.

		0'	30' *	40'	60'	90'
MAP/SVRI	**NS**	140/2117	48/2523	49/2269	38/2812	31/3029
	AO+NS	131/2872	53/3510	136/5703	125/7718	65/7847
	AO+HS	134/2731	50/3363	138/3869	145/5158	114/5725
	AO+HA	134/2301	45/2998	124/1569	130/2948	96/5315
CI/SI	**NS**	5.4/32.8	1.6/11.4	1.8/12.1	1.2/7.5	0.9/4.8
	AO+NS	4.1/24.0	1.2/7.8	1.7/13.0	1.3/8.7	0.7/5.1
	AO+HS	4.0/24.0	1.4/9.4	4.1/35.9	2.9/21.4	1.6/11.8
	AO+HA	4.8/30.2	1.2/10.3	6.2/48.1	3.8/26.4	1.5/10.7
MPAP/PWP	**NS**	8.5/4.5	6.8/1.1	7.7/0.7	7.2/-0.3	7.6/0.4
	AO+NS	8.7/3.5	6.2/-0.3	7.3/1.3	8.5/0.1	5.5/0.8
	AO+HS	16.7/3.7	6.1/0.4	12.3/4.1	10.6/2.9	6.8/0.6
	AO+HA	17.9/5.2	7.9/1.1	18.5/6.2	14.8/4.1	7.6/0.4
HTC/CBL	**NS**	33/0	34/33.9	33/41.1	34/53.8	31/60.9
	AO+NS	35/0	38/36.5	34/42.1	33/49.1	31/59.8
	AO+HS	34/0	36/34.9	26/39.4	26/44.6	27/52.7
	AO+HA	35/0	34/35.2	27/38.5	27/44.3	27/51.7

There were no differences (p>0.01) between groups at basal measures and after 30 min. Cumulative blood loss was similar between the groups. MAP recovered toward basal levels in AO+NS with a marked increase in SVRI, with no increments in CI, SI, MPAP and PWP. In AO+HS and AO+HA, MAP recovery lasted longer, with lower increases in SVRI, while the CI, SI, MPAP and PWP showed marked transient increase.

Conclusion: **We concluded that the injection of both hypertonic solutions after aortic occlusion produced significantly better hemodynamic profiles and should be seriously considered for the first treatment in severe uncontrolled hemorrhagic shock from abdominal source.**

HYPERTONIC-HYPERONCOTIC SALINE DEXTRAN (HHS:7.2%NaCl/10% DX60) IN SEPTIC SHOCK - PRELIMINARY RESULTS OF AN ONGOING CLINICAL TRIAL

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Background: Microcirculatory failure and subsequent focal ischemia is a major cause for development of organ dysfunction, and multiple organ failure in septic shock. It has been demonstrated that bolus infusion of HHS maintains or even increases local blood flow, regional DO_2 and VO_2, and reduces volume requirements in a model of hyperdynamic endotoxemia indicating that HHS infusion may have beneficial effects in patients with septic shock. The present study was designed to investigate the effects of HHS infusion in ICU-patients in septic shock.

Methods: Until now 30 patients have been entered into a controlled, randomized, double-blinded clinical trial with 4 centers participating. Entry criteria: I) Age ≥ 18 years, II) at least two of the following criteria (a-c): a) leukocyte count ≥ 9 G/l or < 3 G/l; b) body temperature > 38°C; c) known or suspected septic focus, III) cardiac index (CI) > 150% of the age-corrected normal value, IV) avDO2 < 5 ml/100 ml. Each patient entered into the study receives 20 ml of monovalent hapten dextran i.v. followed by bolus infusion (within 2 min) of 4ml/kg b.w. of the test-solution. The test-solution contains either HHS or 10% dextran 60 (CGR) in coded infusion bags. Before and 5, 20, 35, 50 and 65 min after bolus infusion hemodynamic (HR, MAP, PAP, CVP, PCWP, CO) and laboratory parameters (pH, pO_2, SO_2, O_2CT, Osmolality, HCT, lactate, Na, K) are measured.

After each new patient results are entered into the database and sequential t-Test analysis for unpaired series is performed (α=0.05, β=0.10). The parameter which determines the stopping rule is DO_2 over a 60 min time period after bolus infusion; for this purpose the ratio of the area under the curve for the control values and for the measurement period are calculated.

The stopping rule is met if (null hypothesis is true) $Fn < \log(\beta/1-\alpha)$ or if (alternative hypothesis is true) $Fn > \log((1-\beta)/\alpha)$.

The stopping rule to finish the trial has not been met yet.

Comment: So far the results of this study show a trend indicating efficacy of HHS in septic shock patients. Final results are expected to be available at time of SALT V.

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HYPERTONIC-HYPERONCOTIC SALINE DEXTRAN (HHS: 7.2%NaCl/10% DEXTRAN 60) INSTANTANEOUSLY RESTORES GUT MUCOSAL BLOOD FLOW (BF).

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Background: It is known that the mucosa of the gut is particularly sensitive to ischemia. In low flow states, e.g. hemorrhagic shock, morphologic changes of intestinal mucosa with subsequent impairment of mucosal barrier function occur in a time dependant manner. Therefore, already primary resuscitation should restore mucosal BF in the entire intestinal tract to limit mucosal barrier damage. Since local mucosal BF varies within the intestinal tract, measurement of global BF in the Superior Mesenteric Artery or in random tissue samples from the gut, may not provide sufficient information about local changes of mucosal BF. In this study, local mucosal BF of the entire gut was determined in shock and after resuscitation with HHS.

Methods: Nine splenectomized beagles under general anesthesia were controlled ventilated and subjected to a standardized trauma followed by hemorrhage to a MAP of 40 mmHg for 75 min. Thereafter the animals were resuscitated with a bolus infuion of 4 ml/kg b.w. of HHS within 2 min, and 35 min later (4 ml/kg) 6% dextran 60 was infused. Hemodynamic parameters and local BF (radioactive microspheres ϕ 15 µm) were measured before (control), at the end of the hypotensive period and 5, 30 and 60 min after resuscitation. After death of the animals the entire gut was dissected into 180 tissue specimens. Thereafter each specimen was separated into mucosal and corresponding sero-muscular compartment resulting in a total of 360 tissue samples (small intestine (SI) 300, colon 60 samples). Radioactivity of the samples was measured in a gamma counter and BF was calculated for each sample ($_{tot}$=mucosal + serosal BF; $_{muc}$=mucosal BF).

Results: Blood flow of the gut is shown on the table (^{Q1}median^{Q3}; ml/min/100g)

Region	control	75'hypo	5'p.Res.	30'p.Res.	60'p.Res
SI_{total}	$^{52}61^{95}$	$^{10}21^{49}$	$^{46}89^{136}$	$^{47}60^{134}$	$^{43}69^{138}$
$Colon_{total}$	$^{42}66^{120}$	$^{16}36^{60}$	$^{23}64^{223}$	$^{48}74^{169}$	$^{39}81^{167}$
SI_{muc} 1st loop	$^{96}115^{130}$	$^{48}59^{78}$	$^{119}147^{188}$	$^{96}121^{143}$	$^{100}117^{152}$
SI_{muc} 2nd loop	$^{88}105^{127}$	$^{38}49^{67}$	$^{103}128^{188}$	$^{81}108^{127}$	$^{84}114^{137}$
SI_{muc} 3rd loop	$^{77}95^{113}$	$^{37}49^{66}$	$^{84}125^{159}$	$^{78}104^{121}$	$^{74}99^{126}$
SI_{muc} 4th loop	$^{71}83^{98}$	$^{42}47^{64}$	$^{98}121^{165}$	$^{73}97^{116}$	$^{71}90^{117}$
SI_{muc} 5th loop	$^{58}79^{92}$	$^{36}44^{53}$	$^{82}115^{148}$	$^{66}86^{109}$	$^{69}93^{115}$
SI_{muc} 6th loop	$^{68}83^{97}$	$^{46}49^{67}$	$^{109}139^{175}$	$^{71}98^{146}$	$^{71}106^{137}$
$Colon_{muc}$ mean	$^{98}143^{234}$	$^{78}93^{122}$	$^{211}260^{348}$	$^{142}183^{255}$	$^{136}179^{264}$
$Colon_{muc}$ distal	$^{88}167^{213}$	$^{56}71^{108}$	$^{171}226^{302}$	$^{84}146^{214}$	$^{103}146^{231}$

Conclusions: This study shows that resuscitation from hemorrhagic shock by means of HHS instantaneously restores mucosal BF in the entire gut and may attribute to prevention of late complications in trauma patients.

HYPERTONIC HYPERONCOTIC SOLUTIONS IN TRAUMATIC BRAIN INJURY WITH ACUTE INTRACRANIAL HYPERTENSION IN RABBITS

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Background: Small volumes of hypertonic/hyperoncotic solutions (HHS) are very efficient to restore cardiovascular function in hemorrhagic shock. Little is known, however, about potential side effects of this treatment on the central nervous system in the presence of a cerebral lesion. Purpose of the current study was, therefore, to analyze the influence of HHS on the increased intracranial pressure (ICP) induced by head injury. The studies were conducted in experimental animals with a focal cerebral lesion and an additional epidural mass, receiving a mixture of 7.2 % NaCl and 10 % Dextran-60 (HHS) i.v. within two min.

Methods: New Zealand albino rabbits (n=6) were anesthetized with α-chloralose, tracheotomized, and artificially ventilated. Arterial and venous catheters were implanted then for blood pressure recording and administration of fluid and drugs. An epidural screw was inserted into a 2 mm Ø burr hole of the right hemicranium for continuous measurement of ICP. An epidural balloon was introduced then between the brain surface of the left hemisphere and the skull. A cryogenic lesion of the exposed brain surface was made by a stainless steel cylinder probe for 120 sec, which was cooled by liquid N_2. Thereafter, the cranial cavity was closed by reimplantation and resealing of the piece of skull bone removed for trephination. 60 min later the balloon was inflated by physiological saline until the ICP increased to 15 mmHg. Expansion of the balloon was maintained during the whole experiment.

Results: During control conditions the ICP was 3±1 mmHg. Induction of the cold lesion of the brain together with inflation of the balloon led to an increase of the ICP to 15 mmHg, while the subsequent bolus of HHS (4 ml/kg b.w.) to a marked reduction back to the control level. Subsequently, however, ICP rose again to 15 mmHg within 88±17 min. Another administration of HHS in the same dose resulted in a less pronounced decrease of the ICP (9±1 mmHg) followed by an increase to 15 mmHg within 74±17 min. The plasma Na^+-concentration was increased from 165±3 to 180±2 mM/l after the first bolus of HHS, repetition of the same dose led to an increase to 187±2 mM/l. Recovery of the enhanced plasma Na^+-levels to normal occurred within 30 or 60 min, respectively.

Conclusions: Taken together, the current findings demonstrate effectiveness of HHS to lower the increased ICP from a focal brain lesion and an intracranial mass, while evidence on adverse side effects was not obtained. The increased plasma Na^+-concentration was found to recover spontaneously within 60 min at the latest. The present experiments make promising further studies towards development of a treatment protocol for patients with intracranial hypertension from severe head injury.

THE EFFECT OF HYPERTONIC SALINE ON MYOCARDIAL CONTRACTILITY IN ANESTHETIZED PIGS

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Background: The beneficial hemodynamic effects of hypertonic saline (HS, 7.5% NaCl) have been attributed to increased preload, systemic arterial vasodilation, and increased myocardial contractility. The purpose of this study was to accurately determine the inotropic effects of HS as assessed by left ventricular (LV) end-systolic elastance (Ees), a relatively load-independent index of myocardial contractility.

Methods: Pigs were anesthetized with isoflurane in O_2 by facemask, and their tracheas were intubated. Ventilation was controlled to maintain arterial CO_2 tensions at ~ 40 mmHg. The carotid and femoral arteries, and jugular and femoral veins were surgically exposed and isolated. Catheters were placed for hemodynamic measurements, LV pressure (Millar Instruments), and volume (conductance catheter) determinations. Ees was determined during transient (8 to 10 s) caudal vena caval balloon occlusion. Following instrumentation, the isoflurane concentration was reduced and maintained at a constant end-tidal concentration (1 minimum alveolar concentration, 1.5%). Pigs were randomly administered either 0.9% NaCl (n=7) or HS (n=9) at a dose of 4 mL/kg, over 3 min into the right atrium. Hemodynamic and LV pressure-volume measurements were made for 60 min.

Results: Myocardial contractility, as measured by Ees, did not change in either treatment group. The rate of change of LV pressure (dP/dt_{max}) increased significantly ($P < 0.05$) at 5 min after treatment with HS. LV end-diastolic volume increased significantly from 5 to 30 min following treatment with HS. Central venous and pulmonary capillary wedge pressures, and cardiac index increased significantly at 5 min after treatment with HS.

Conclusion: These results suggest that HS is not a positive inotrope in the anesthetized pig and that increases in cardiac index are primarily due to an increased preload.

EFFECTS OF HYPERTONICITY ON HYPOXIC RABBIT MYOCARDIAL INTRACELLULAR SODIUM AND CALCIUM

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Background: We have previously reported that hypoxia-induced increases in rabbit myocardial Na and Ca appear to be the result of increased pH-regulatory Na-H exchange which leads to the collapse of the membrane Na gradient and eventually Ca entry via Na-Ca exchange (Am J Physiol 259:C940-948, 1990). Studies using model systems suggest that hypertonicity is able to reduce or prevent pH-regulatory Na-H exchange (Cala, *et al*, Comp Physiol Biochem, in press). Therefore, we initiated studies to test the hypothesis that hypertonic perfusion will minimize Na^+ uptake and consequently, reduce Ca^{++} accumulation in hypoxic myocardium.

Methods: ^{23}Na and ^{19}F NMR spectroscopy with DyTTHA (15mM) and 5-FBAPTA (5uM) were used to measure intracellular Na content (Na_i) and Ca concentration ($[Ca]_i$), respectively, in 35 isolated Langendorff-perfused adult rabbit hearts with a fixed perfusion rate. Control solution was HEPES buffered Krebs-Henseleit solution (K-H, 295 mOsm) and hypertonic solution was K-H plus 30 additional milli-osmoles of NaCl (325 mOsm). Baseline data were collected with perfusate equilibrated with 100% oxygen (30 minutes) and hypoxia was achieved with perfusate equilibrated with 100% nitrogen (60 minutes.)

Results: After one hour of hypoxia, $[Ca]_i$ increased by 66% from 407 ± 23 to 676 ± 124 nM ($n = 5$, $p < 0.05$). When Na efflux was blocked during hypoxia by removal of perfusate K^+ (ie, inhibiting Na/K-ATPase), Na_i increased from 8 ± 2 to 89 ± 9 mEq/kg dry weight ($n = 6$, $p < 0.05$), and $[Ca]_i$ increased 4 fold to 1306 ± 89 nM ($n = 6$; $p < 0.01$). When Na influx was inhibited by ethylisopropylamiloride (EIPA, 100 uM), a specific inhibitor of Na-H exchange, both Na_i and $[Ca]_i$ remained essentially unchanged during hypoxia. When the myocardium was exposed to hypertonic perfusion 5 minutes prior to and during K^+-free hypoxia, the observed increase in Na_i was reduced by 58% (38 ± 5 vs 89 ± 9 mEq/kg dry wt, $n = 5$, $p < 0.05$) and the $[Ca]_i$ accumulation by 45% (744 ± 23 vs 1306 ± 89 nM; $n = 6$ for each group, $p < 0.01$.) We have also measured qualitatively similar effects of hypertonic perfusion on Na_i and $[Ca]_i$ in hypoxic newborn rabbit hearts. Results are mean ± 1 SEM, with p values determined by one-way ANOVA.

Conclusions: These results are consistent with the hypothesis that hypertonic perfusion before and during hypoxia reduces Na and Ca loading, and therefore, is able to limit hypoxic cell damage caused by high $[Ca]_i$. The mechanism by which hypertonicity exerts its effects may be explained, in part, by the hypothesis that rabbit myocardial Na-H exchange responds to pH and cell volume changes in such a fashion that volume pertubation precludes pH-regulatory Na uptake during hypoxia, leading to less Ca entry via the Na-Ca exchange.

7.5% SODIUM CHLORIDE-6% DEXTRAN-70 FLUID RESUSCITATION OF HEMORRHAGIC DEHYDRATED SHEEP

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Background: Very small volumes of 7.5% NaCl-6% Dextran-70 solution (HSD) are effective in rapidly resuscitating hemorrhagic animals, in part, due to the rapid expansion of plasma volume by osmotically shifting intracellular fluid into the vascular space. These physiologic actions of HSD, however, may not be effective when the animals have already been dehydrated. Furthermore, there have been concerns that such fluid shift following HSD injection may even be harmful. This study was performed to test the hypothesis that HSD is effective and is without long-term adverse effects in resuscitation of hemorrhagic dehydrated animals.

Methods: Adult sheep were prepared with pulmonary and peripheral arterial catheters, external jugular venous line, and a Doppler flow probe in the left renal artery. Data were collected prior to and after 4 days of dehydration by thristing. Two hours of hemorrhagic hypovolemia were induced by bleeding the animals to a MAP of 50 mmHg. Fluid resuscitation was either HSD (4mL/kg bolus) or lactated Ringer's (LR; 37 mL/kg bolus.) The animals were monitored for two hours after injection, then shed blood was returned. Post-hemorrhage data were collected seven days later on euvolemic animals.

Results: Mean ± 1 SEM, n = 5 in each group, with ANOVA.

Parameters	Fluid	Baseline	Deh	Hem	Res/1hr	Res/2hr	Post Hem
C.O.	HSD	5.7 ± .3	3.9 ± .6	2.1 ± .2	4.1 ± .2	3.9 ± .2	5.9 ± .6
(L/min)	LR	5.5 ± .5	3.6 ± .3	2.0 ± .1	3.5 ± .2	3.2 ± .2	6.4 ± .2
MAP	HSD	85 ± 2	85 ± 1	53 ± 2	86 ± 4	82 ± 5	81 ± 4
(mmHg)	LR	86 ± 3	84 ± 4	52 ± 1	79 ± 4	71 ± 3	90 ± 5
Osmolality	HSD	310 ± 2	327 ± 3	333 ± 7	343 ± 11	343 ± 6	303 ± 3
(mOsm)	LR	312 ± 2	329 ± 4	332 ± 4	326 ± 4	326 ± 4	302 ± 6
Serum Na	HSD	151 ± 1	157 ± 2	158 ± 3	168 ± 6	165 ± 2	152 ± 4
(mEq/L)	LR	153 ± 3	158 ± 4	157 ± 2	156 ± 2	158 ± 3	152 ± 2
Serum Cr	HSD	0.9 ± .1	1.2 ± .1	1.4 ± .1	1.3 ± .1	1.2 ± .1	0.9 ± .1
(mg/dL)	LR	0.9 ± .1	1.2 ± .2	1.5 ± .1	1.4 ± .1	1.2 ± .2	0.9 ± .1
FeNa	HSD	1.76 ± .9	.05 ± .02	.07 ± .02	.42 ± .29	.12 ± .05	1.78 ± .69
(%)	LR	1.61 ± .8	.15 ± .06	.11 ± .05	.20 ± .05	.09 ± .03	2.96 ± .46
Urine flow	HSD	1.45 ± .2	.27 ± .05	.09 ± .06	.66 ± .23	.37 ± .09	1.77 ± .30
(mL/min)	LR	1.58 ± .6	.25 ± .02	.06 ± .02	.43 ± .08	.27 ± .06	2.49 ± .34

Conclusions: 1) HSD resuscitation is very effective following hemorrhage in dehydrated sheep; 2) The osmotic shift of intracellular fluid into the vascular space induced by HSD does not appear to have any long-term adverse effect on cardiovascular or renal functions; 3) Changes in serum osmolality and sodium concentration after HSD injection in dehydrated animals are predictable, as they are in hydrated hemorrhagic animals; 4) HSD is, therefore, an effective and safe resuscitative fluid in hemorrhagic dehydrated animals.

MECHANISM OF THE ACUTE AND INFUSION-RATE DEPENDENT HYPOTENSION INDUCED BY HYPERTONIC SALINE

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Background: Small volumes of 7.5% hypertonic saline (HTS) have been found effective for resuscitation from circulatory shock. When administered rapidly, HTS can cause an acute and brief hypotension prior to the improvement of cardiovascular function. The mechanism by which HTS causes this hypotension remains obscure. The present study was designed to examine the possible roles of the autonomic nervous system (ANS), endothelium-derived relaxing factor (EDRF), and myocardial contractility in mediating the transient fall in the mean arterial pressure (MAP).

Methods: In 16 anesthetized dogs, the left ventricle (LV) was instrumented with pressure and dimension transducers for the assessment of myocardial contractility. Ultrasonic flow probes were used for continuous monitoring of cardiac output (CO) and coronary blood flow (CBF). Hypertonic saline at 3 $ml \cdot kg^{-1}$ was infused at various rates ranging from 0.5 to 3.0 $ml \cdot kg^{-1} \cdot min^{-1}$ before and after pharmacological blockade of ANS or EDRF.

Results: Infusion of HTS at 2.0 $ml \cdot kg^{-1} \cdot min^{-1}$ abruptly decreased MAP from 97 $\pm$ 6 to 61 $\pm$ 4 mmHg ($p < 0.05$). This hypotension was brief (80 - 120s), and accompanied by significant increases in CO (+32 $\pm$ 6%) and CBF (+83 $\pm$ 8%). Concomitantly, percent of systolic shortening of the LV freewall increased by 12 $\pm$ 7%, suggesting an improved myocardial contractility. The acute hypotension induced by HTS was more severe at a higher infusion rate, and could be avoided when HTS was infused at $\leq$ 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$. This hypotension was unaltered by ANS blockade, but it was attenuated by EDRF blockade.

Conclusions: Rapid infusion of HTS was associated with an acute and transient hypotension that was independent of the ANS. The initial fall in blood pressure was not mediated by a depression of myocardial contractility. The fact that this hypotension was attenuated by EDRF blockade suggests that a direct endothelium-dependent mechanism may be involved in the vasodilator effect of HTS. Hypertonic saline should be administered slowly to avoid the acute hypotension that may exacerbate the pre-existing injury.

HISTAMINE RELEASE AND CARDIAC CONTRACTILITY CHANGES FOLLOWING HYPERTONIC SALINE INFUSION

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Background: Small volumes of hypertonic (7.5 %) saline (HS) applied for resuscitation from hypovolemia effectively restore cardiovascular function and have a vasodilator effect. Few data are available on the possible role of vasodilator mediators in this process. Cardiac tissue contains a large amount of histamine (HIS), an autacoid with inotropic and vasodilator effects. HIS could possibly play a role in the vasodilatation and increased cardiac contractility observed after HS infusion The present study sought to examine whether there are changes in HIS content of the plasma and myocardium following infusion of HS.

Methods: The experiments were performed on pentobarbital-anesthetized normovolemic thoracotomized mongrel dogs of both sexes. Mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), cardiac output (CO, electromagnetic flowmeter), blood gases, plasma renin activity (PRA, radioimmunoassay), HIS in blood plasma and heart tissue (radioenzymatic assay) were measured. Left ventricular contractility (LVC) was estimated from the end-systolic pressure-diameter (ESPD) relationship by monitoring left ventricular pressure (LVP) with a catheter-tip micromanometer and left ventricular diameter with a pair of ultrasonic crystals sutured on the myocardium. Pressure-diameter loops were obtained during transient vena caval occlusions with a balloon catheter. The slopes of the ESPD relationship were calculated with a computer program. 4 ml/kg HS (Group I, n=11) or 8ml/kg HS (Group II, n=11) was infused i.v. in 15 minutes. Hemodynamic parameters were recorded and blood samples taken before infusion and at several later time points. In an additional 43 animals only left ventricular tissue HIS was measured before and after an infusion of 4ml/kg or 8 ml/kg HS.

Results: Infusion of corresponding volumes of 0.9% NaCl had no effect on the measured variables. There was no elevation of PRA following the surgical procedure. After infusion of both doses of HS a transient increase in MAP, LVP, CVP, CO and a decrease in hematocrit and PRA was observed. In Group I an increase in LVC from 30.2 ± 5.5 to 46.4 ± 15.3 mmHg/mm (mean ± semi-interquartile range) occurred lasting about 30 min and simultaneously plasma HIS elevated from 1.25 ± 0.6 to 3.84 ± 1.1 nmol/L. In Group II the changes in LVC (from 26.7 ± 5.2 to 34.2 ± 6.1) and HIS (from 0.87 ± 0.7 to 2.37 ± 1.29) were less and in the case of LVC statistically not significant. Both doses of HS increased myocardial HIS (Group I: from 3.12 ± 0.4 to 4.22 ± 0.7 , Group II from 3.06 ± 0.35 to 4.1 ± 0.8 nmol/g).

Conclusion: 4ml/kg or 8ml/kg HS infused into dogs causes a release of HIS detectable in the plasma and an increase of myocardial HIS content (the latter suggesting increased HIS synthesis in the heart). HIS could play a role in the vasodilatation and increased LVC following HS infusion. Absence of LVC increase after the larger dose may be due to a dehydrating effect on the heart.

HYPERTONIC-HYPERONCOTIC RESUSCITATION FROM HEMORRHAGIC SHOCK EFFECTIVELY IMPROVES INTRAMUCOSAL ACIDOSIS

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Background: Fiddian-Green has recently introduced the tonometric technique to monitor gut intramucosal ph (pHi). This non-invasive technique uses an intraluminally placed silicone balloon catheter for measurement of intraluminal pCO_2 which allows calculation of pHi by a modified Henderson-Hasselbach equation.
Resuscitation with hypertonic-hyperoncotic saline dextran (HHS: 7.2% NaCl/ 10%Dextran60) has proven to restore central hemodynamics and local blood flow after hemorrhagic shock. Intramucosal acidosis is known to be paralleled by impairement of mucosal barrier function leading to Gut-Derived Infectious-Toxic Shock or Multiple Organ Failure. The aim of this study was to investigate the effects of HHS on intramucosal acidosis in hemorrhagic shock by means of tonometry.
Methods: 8 anesthesized beagles were subjected to a standardized trauma and bled to a MAP of 40mmHg for 75 min. At the end of hypotension a bolus of HHS (4 ml/kg b.w.) was given in 2 min. 35 min later an additional bolus of 4 ml/kg 6%Dextran 60 was administered. Hemodynamic parameters, local mucosal blood flow (BF) and pHi were measured before hemorrhage (control), at the end of hypotension, as well as 30 min and 60 min post HHS resuscitation. Via enterostomy two tonometer catheters were positioned in the small intestine, one in the jejunal lumen (pHi/prox) and the other in the ileal lumen (pHi/dist). Local mucosal blood flow (BF/prox and BF/dist) in the gut segments surrounding the tonometer balloons (length of segments: 14cm each) was assessed using the microspheres technique (radioactive microspheres ϕ 15µm).
Results: Data obtained are shown in the following table (Mean±SD, n=8):

	Control	End Hypo	30min Res	60min Res
AOP mmHg	105±7.0	40±1.4	78±11.2	85±14.5
CI l/min/kg	1.73±0.26	0.48±0.14	1.72±0.20	1.64±0.26
DO_2 ml/min/kg	263±48.5	48±10.0	143±14.4	137±15.5
BF/prox ml/min/100g	122±35	57±13	118±27	128±37
pHi/prox	7.30±0.07	6.81±0.19	6.98±0.14	7.11±0.10
BF/dist ml/min/100g	110±22	52±11	103±21	113±34
pHi/dist	7.32±0.10	6.79±0.19	6.98±0.12	7.10±0.08

Conclusion: HHS resuscitation from hemorrhagic shock normalizes mucosal blood flow and improves mucosal pHi; we assume that both effects have beneficial influence on mucosal barrier function and translocation.

THE EFFECT OF HEATING ON HYPERTONIC SALINE TREATMENT OF UNCONTROLLED HEMORRHAGIC SHOCK (UCHS).

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Background: Hypertonic saline treatment of UCHS leads to increased bleeding, hemodynamic deterioration and increased mortality. The effect of heating on this response was studied in rats.

Methods: The animals were divided into 2 groups: gr. I (n=30) UCHS was induced by 20% rat tail resection. gr. II (n=30) UCHS after 5h of heating at 37 C. Each group was then divided into 4 treatment subgroups: a - untreated; b - 5 ml/kg NaCl 7.5% (HTS); c - 41.5 ml/kg NaCl 0.9% (NS); d - HTS+NS, and the animals observed for 4 hours.

Results: Tail resection in gr.Ia was followed by bleeding of 4.7±0.4 ml and fall in mean arterial pressure (MAP) to 44±5 torr in 15 min, while in gr.IIa bleeding was 3.7±0.5 ml ($p<0.05$) and MAP dropped to 59±6 torr ($p<0.05$). HTS infusion in gr.Ib was followed by bleeding of 3.5±0.4 ml and fall in MAP to 35±0.8 torr after 60 min, while in gr.IIb blood loss in response to HTS was 2.0±0.4 ml ($p<0.05$) and MAP was 67±8 torr ($p<0.05$). NS infusion in gr.Ic was followed by bleeding of 4.8±0.8 ml and increase in MAP to 68±6 torr in 60 min while in gr.IIc bleeding was 4.5±0.9 ml and MAP fell to 51±8 torr ($p<0.05$). Infusion of HTS+NS in gr.Id resulted in bleeding of 4.4±0.5 ml and increase in MAP to 83±8 torr, while in gr.IId blood loss was 2.9±0.9 ($p<0.05$) and MAP increased to 72±8 torr ($p<0.05$).

Conclusions: Blood loss in response to injury and to HTS infusion is reduced following heating. The HTS and NS combination induced a better hemodynamic response in normal rats compared to heated animals.

HYPERTONIC - HYPERONCOTIC SOLUTIONS AND INCREASED INTRACRANIAL PRESSURE (ICP).

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INTRODUCTION: Hypertonic-hyperoncotic solutions (HHS) have proven to be an excellent fluid regime in resuscitation of hypovolemia due to trauma, hemorrhage and shock. However it is not clarified whether these solutions are safe in patients with head trauma and increased intracranial pressure (ICP) too.
METHODS: The study was done in 12 splenectomized sheep. In general anesthesia surgical preparations of arteries and veins (for monitoring blood pressure, plasma volume changes) were performed; then two holes were drilled in the skull (for measuring ICP). After reaching a stable phase sheep were bled 35 ml / kg to a mean arterial pressure of 40 mm Hg. At the same time a balloon was placed in the epidural space and filled with saline to increase ICP from 6 mm Hg up to 30 mm Hg.Then sheep were divided into two groups: After a further period of 30 minutes either Ringer's solution 8 ml / kg or HHS (7.2% NaCl - 10% HES 200 / 0.5) 4 ml / kg were given as bolus within 3 minutes. Measurements were done up to two hours after the end of fluid resuscitation.
RESULTS: Immediately after the end of infusion MAP increased from 40 mm Hg to 95 mm Hg; 30 min after the end of infusion MAP was 102 mm Hg; this parameter remained stable during the observation period. Plasma volume increased up to 20 ml / kg after the end of HHS application; during the following period a slight decrease of plasma volume was seen; two hours after the end of infusion the increase in plasma volume was 17 ml / kg.
Immediately after the end of infusion ICP decreased from 30 mm Hg to 20 mm Hg; during the following period ICP showed a further decrease and 1 hour after the end of infusion ICP was within a normal range (4 - 8 mm Hg). Histological evaluation did not show any deleterious influence of HHS on tissues.
In the Ringer's group there was only a temporary increase of mean arterial blood pressure up to 85 mm Hg; during the following observation period blood pressure decreased to 60 mm Hg and remained stable at these value for the following time. In contrast to the HHS group ICP did not show any tendency to decrease in the Ringer's group, however a slight, but not significantly increase of ICP up to 33 mm Hg was seen.
CONCLUSIONS: A rapid increase of mean arterial pressure accompanied by an increase in plasma volume make these solutions an ideal fluid for initial treatment of hypovolemic shock. As seen in our study hypertonic-hyperoncotic solutions decrease elevated ICP without any negative influence on brain tissue. Our results lead to a previous recommendation that HHS can be safely applicated in patients presenting with head trauma, increased ICP and hypovolemic shock.

EVALUATION OF AN INTRAOSSEOUS PUNCTION VERSUS INTRAVENOUS AND CENTRAL CATHETER IN PATIENTS WITH HEMORRHAGIC SHOCK

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Background:
A safe and rapid vascular access in victims of traumetic shock is imperative for the patient's survive. Intraosseous infusion of the sternum has been recognized as an alternative route of vascular access.
We compare the velocity of access, fluid infusion and blood pressure response between four different solutions (plasma, dextran 40, Hypertonic/hyperosmotic and crystalloid) by either intraosseous, intravenous or central catheter.

Methods:
100 consecutive patients with hypovolemic shock due to different causes were ramdomly asigned for receive 300 ml of plasma, 500 ml of dextran, 250 ml of Hypertonic saline dextran solution (H/H) or 1000 ml of isotonic crystalloid by either intraosseous (51), intravenous (34) or central catheter (20); We analysed velocity of access route, fluid infusion & blood pressure on entry and 30 minutes after.

Results:
There were no differences in age, gender or cause of hemorrhage. Velocity of access, fluid infusion were differences be--tween solution and vascular route (Table I)

	Intraosseous	Intravenous	Central
	(minutes)		
Crystalloid	14±7*	35±12**	25±10
H/H	17±9*	-----	25±8**
Plasma	9±7*	40±27**	14±3
Dextran 40	16±3*	38±8 **	20±7
Access time	2±1.3	3±1.6	5.5±2.5

* vs ** = p - 0.05 ; X±SD

There was no difference in Blood pressure between groups at the beginning of the study, however we could find significant increase of blood pressure 30 minutes after infusion without differences between solutions except for the intraosseous infusion (p- 0.05)

Conclusion:
We suggest that intraosseous punction via sternal marrow space might be rapidly and safe performed with H/H solution better than peripheral or central catheter in patients with hemorrhagic shock.

COMPARISON OF DIFFERENT HYPERTONIC FORMULATIONS ON THE CONTRACTILITY OF ISOLATED MYOCARDIUM

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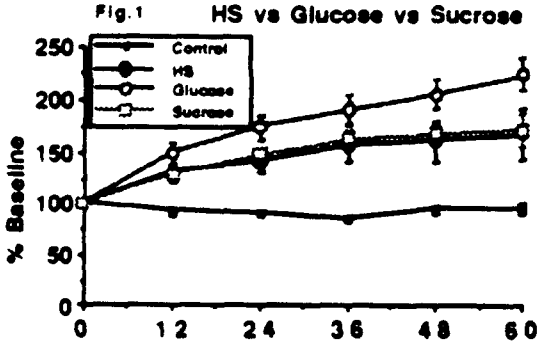
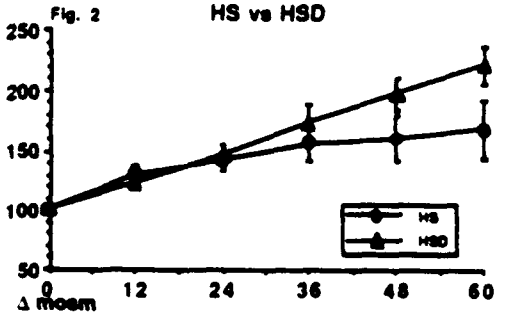
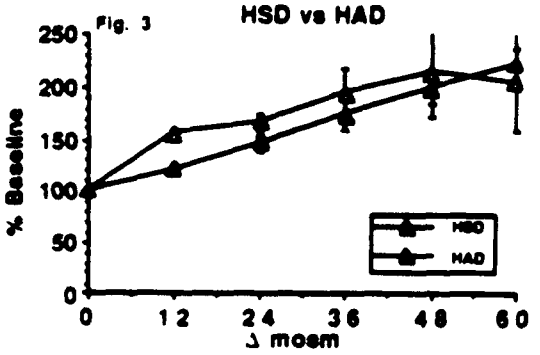
Background: Small volume (4-5 ml/kg) infusions of hyperosmotic saline (HS) can improve hemodynamic performance in shock and increase serum osmolarity 20-30 mosm. Part of the improvement in hemodynamic conditions due to HS has been attributed to a direct or indirect cardiac effect. In the present study, we examined how several different hypertonic solutes affected the contractile properties of isolated rabbit papillary muscles.

Methods: Right ventricular papillary muscles were isolated from pentobarbital anesthetized rabbits and suspended in muscle baths containing Krebs bicarbonate solution at 36° C. The papillary muscle was paced at 12 beats/ minute using field electrodes from a Grass stimulator. Continuous infusion and replacement of the incubation medium was accomplished at the rate of 5 ml/ minute. After the initial stabilization of the contractile responses to electrical stimulation, the medium was altered by 12 mosm increments at 45 min. intervals from 300-360 using the following solutes: 1. Hypertonic sodium chloride (HS); 2. Hypertonic sodium chloride + Dextran (HSD); 3. Hypertonic sodium acetate + Dextran (HAD); 4. Glucose; 5. Sucrose.

Results: Figures show plots of steady state increase in osmolarity *vs.* developed tension (% baseline, g/mm^2). Glucose provided greater inotropic responsiveness than Sucrose and HS. Control muscles maintained in regular medium showed no significant alteration in contractile force during the course of the experiment, Fig.1. Increased inotropy was also produced by HS and HSD. HSD appeared to an enhance contractility compared to HS above the range of 36 mosm, Fig 2. HSD and HAD produced similar increases in contractile force, Fig. 3.







Conclusion: Increased osmolarity due to HS, HSD and HAD in the clinically relevant range showed definite positive inotropy. Hypertonic glucose may provide greater inotropic stimulation than hypertonic saline or other metabolizable solutes.

TREATMENT OF HYPERTHERMIA AND DEHYDRATION WITH HYPERTONIC SALINE IN DEXTRAN (HSD).

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Background: Hyperthermia may be accompanied by dehydration with the loss of electrolytes (sweat loss in man or saliva spread in rats for evaporative cooling) or without electrolyte loss (water deprivation). Thermally-induced sweat loss in man and saliva loss in rats both result in electrolyte loss, increased serum osmolarity, and dehydration.
Methods: Wistar-Furth rats (300g, male) which do not have an anaphylactoid reaction to dextran were used to determine the efficacy of hypertonic saline in dextran solution (HSD, 7.5% NaCl in 6% dextran 70) for the treatment of heat stroke. Rats were deprived of water for 24 hr (DE) or not (ND), heat-stressed restrained (RE, to prevent saliva spread) or unrestrained (NR), and 4 ml/kg of saline (SAL) or HSD was administered via tail vein at the end of heat stress (a core temperature of 42.3°C). The following 8 groups of 10 rats each were used: SALNDRE, SALNDNR, SALDERE, SALDENR, HSDNDRE, HSDNDNR, HSDDERE, and HSDDENR.
Results: Rats that were DE had significantly ($p<0.05$) higher heating rates (rates of rise of core temperature) and less water loss during heat than ND rats, but hydration status was not correlated to 24 hr survival with a 42.3°C endpoint. Rats that were RE had significantly less weight loss, less thermal area, and higher cooling rates than NR rats; but, there was no significant difference in 24 hr survival between RE and NR groups. HSDNDNR (90 vs 60%) and HSDDERE (90 vs 40%) groups had significantly higher survival rates than their corresponding SAL groups; there was no significant difference in survival between the HSDNDRE (70 vs 60%) and HSDDENR (70 vs 60%) groups and their corresponding SAL groups.
Conclusion: Therefore, in heat-stressed rats, HSD administration is more beneficial for the treatment of heat stroke than SAL regardless of hydrational status.

DELIBERATE FLUID RESTRICTION IN POST TRAUMATIC HYPOVOLEMIC HYPOTENSION

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Background: Current approaches to fluid resuscitation, including hypertonic fluids, are based principally on "controlled hemorrhage" animal models. Clinical controlled comparisons in the urban setting of no fluid resuscitation, versus isotonic or hypertonic fluid resuscitation are scant. The thesis that hypotension may actually be teleologically protective requires investigation. Numerous historic and current clinical anomalies even support this hypothesis.

Methods: A prospective, controlled trial comparing a restricted fluid resuscitation versus "routine" EMS and Emergency Center (EC) fluid resuscitation in penetrating urban trauma continues.

Results: Preliminary analysis of the initial 300 patients reveals: 1) Well matched groups, 2) identical field, EC, and hospital times, 3) decreased fluid and blood requirements in the restricted fluid group, 4) decreased ICU stay and complications in the restricted fluid group, and 5) better survival rate in the fluid restricted group. Renal failure, ARDS, multi-organ failure and overwhelming sepsis was NOT seen in the fluid restricted group. Patients with penetrating truncal trauma and an initial blood pressure of $\leq$ 90/- were eligible for inclusion. All treatments were identical except for fluid restriction until skin incision in the study group.

Conclusion: These data suggest that aggressive preoperative fluid resuscitation in the patient with urban penetrating trauma may actually be detrimental. Attempts to maximize oxygen delivery rather than reversing hypotension may be the optimal objective in treatment of post traumatic hypotension.

TITLE: EFFECTS OF HYPERTONIC SALINE DEXTRAN ON INTRACRANIAL PRESSURE AND BRAIN WATER DURING CARDIOPULMONARY BYPASS

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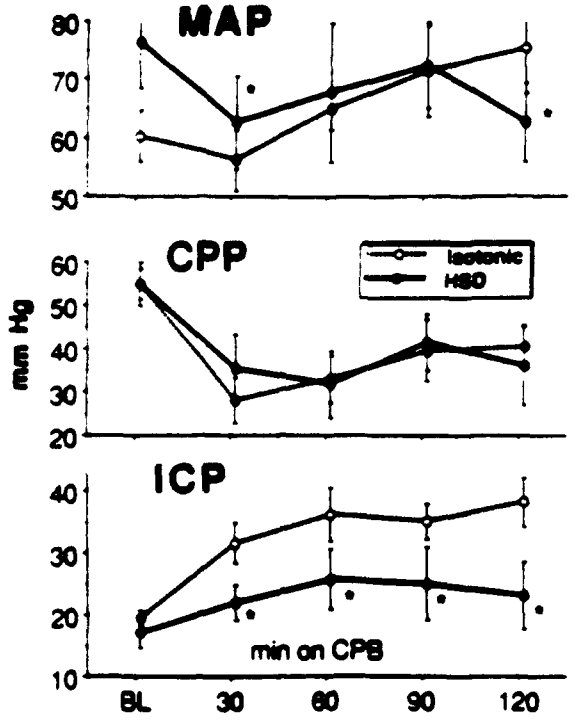
Intracranial pressure (ICP) rises during cardiopulmonary bypass (CPB) in human adults, infants,[1,2,3] and experimental animals.[4] Reduced mean arterial pressure (MAP) with elevated ICP during CPB results in decreased cerebral perfusion pressure (CPP). Hypertonic saline lowers ICP in children with head trauma[5] and in animal resuscitation.[6] Hypertonic saline Dextran (HSD) mobilizes intracellular and interstitial water in resuscitation models.[7] We hypothesized that HSD lowers ICP and reduces brain water in normothermic CPB swine models.

METHODS: Twelve swine (30-40 kg) were anesthetized with isoflurane. Vascular catheters and subdural Richmond bolts were inserted. Animals were assigned to one of two priming solution groups. Isotonic Group (n=6) 1000 ml Ringer's lactate + 500 ml hetastarch. HSD Group (n=6) 1000 ml Ringer's lactate + 500 ml hetastarch + 1 ml/kg 25% NaCL/24% dextran. CPB was instituted with bicaval and aortic cannulae for 2 hours at flows of 85-100 ml/kg/hr. Baseline and CPB hemodynamic and ICP measurements were made. Tissue samples were taken after sacrifice.

RESULTS: ICP increased during CPB in both groups. ICP increased significantly less in HSD group at all points during CPB ($p<0.05$). MAP decreased from baseline in both groups after CPB initiation but MAP decreased significantly more in HSD group at 30 and 120 min CPB ($p<0.05$). CPP decreased (CPP = MAP-ICP) during CPB for both groups. No differences in brain water (wet/dry analysis) were found. Data ± SEM: $p<0.05$ using paired Student's t-test. (* = $p<0.05$)



DISCUSSION: CPP is reduced during CPB due to increased ICP and reduced MAP. We have shown that HSD minimizes ICP increases during CPB without changing brain H_2O. We have also shown that HSD does not improve CPP despite lower ICP because of attendant lower MAP. Effects of HSD to lower MAP during CPB may be due to vasodilating properties of HSD. Use of HSD in the prime solution of CPB effectively reduces ICP, however, no improvement in CPP was noted.

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CONTINUOUS SMALL VOLUME RESUSCITATION WITH HYPERTONIC SALINE DEXTRAN SOLUTION IMPROVES SURVIVAL IN EXPERIMENTAL SEPSIS

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Background: Adequate volume resuscitation is an essential component of successful therapy of septic shock. Resuscitation with either crystalloid or colloid solutions leads to fluid retention, peripheral edema and often pulmonary edema. An ideal regimen would cause sustained effective hemodynamic function without peripheral or lung edema. Several studies suggest, that small volume resuscitation with hypertonic saline/dextran solutions may offer therapeutic advantages. In the present study we investigated the effects of hypertonic saline dextran solution (7.5% NaCl/ 6% dextran-70, HSD) in a lethal model of sepsis.

Methods: Twelve chronically instrumented sheep received continuous infusion of endotoxin (10 ng/kg/min). Volume resuscitation was performed by continuous infusion of either HSD (0.5 ml/kg/h) or lactated Ringer's solution (RL, 5 ml/kg/h) over 24 h. Additional RL in either group was given when the left atrial pressure (LAP) was < 2mmHg or hematocrit > 35%.

Results: HSD significantly reduced mortality (1/6 in the HSD group vs. 5/6 in the RL group). In both groups, the first 4 h after start of the endotoxin infusion were characterized by hemodynamic instability. Two animals died in this period, one in each group. During this period, the HSD group had lower O_2-extraction ratios. After 8 h, two more of the control animals died in association with a low cardiac output syndrome. The survivors showed increasing cardiac outputs. The HSD animals developed a hyperdynamic situation with elevated cardiac outputs, decreased systemic vascular resistances, and increased pulmonary shunt fractions. After 16 h, two more of the control animals died with cardiac output slightly above baseline levels. The one survivor of the control group showed only minor changes in response to the endotoxin infusion. Both groups required additional fluid (either oral or iv) to maintain hematocrit and/or left atrial pressure in defined ranges. All but one animal of the HSD group drank water spontaneously and did not receive additional fluid intravenously. The administration of HSD prevented fluctuation of the potassium levels observed in the RL group. The maximal sodium level measured was lower than 157 mEq/l.

Conclusion: Hypertonic saline/dextran solution significantly reduced mortality in a lethal model of sepsis. No single mechanism responsible for the improved outcome could be identified. The requirement of additional fluid in the HSD group suggests, that lower concentrated salt solution may offer advantages over the composition used in the present study.

COMPARISON OF RESULTANT ACID-BASE BALANCE AFTER SMALL VOLUME RESUSCITATION WITH HYPERTONIC SALINE/DEXTRAN OR HYPERTONIC ACETATE/DEXTRAN

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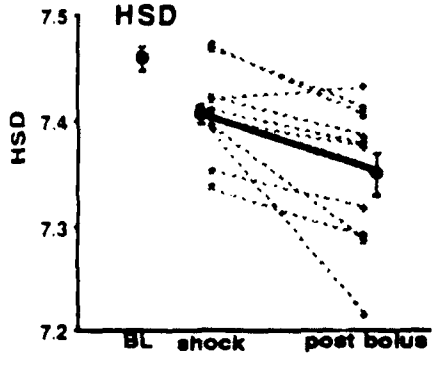
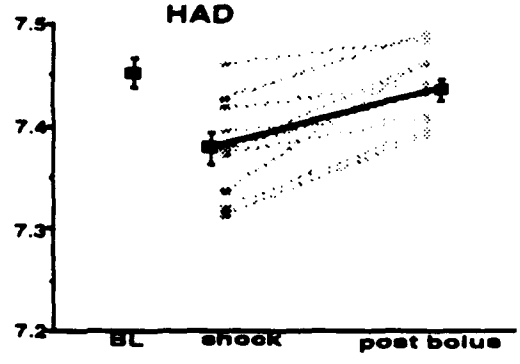
Background: To date, the only reported contraindication in clinical trials using hypertonic saline has been a hyperchloremic acidosis (Vassar, 1990) suggesting that resuscitation with 2400 mosm NaCl/6%-dextran 70 (HSD) may be contraindicated in patients with a severe, pre-existing acidemia.

Methods: In the present study, we compared the resuscitative effects of HSD with a hypertonic, 2400 mosm NaCl-NaAcetate/6%-dextran solution (HAD) in hemorrhaged, acid-challenged, anesthetized swine. Animals were subjected to 90 min of hemorrhagic hypotension (50-55 mm Hg) along with an acid infusion (HCl or lactic acid) given during the last 60 min of hemorrhage. The HAD used in this trial was 7 osmolar parts Na-acetate and 1 osmolar part NaCl. Animals were treated with either 4 ml/kg of HSD (n=10) or HAD (n=10). Thereafter, both groups received isotonic lactated Ringers (LR) to maintain baseline cardiac output (CO).

Results: CO was well-maintained in both groups, with minimal LR requirements. The figures indicate the pH change for each of the individual animals in the 2 groups with the thick solid line indicating mean ±SEM. At the end of shock, both pH and base excess (BE) were below baseline in each group. HSD caused a further immediate decrease in both parameters with pH decreasing from 7.402 to 7.345 and BE decreasing from 1.1 mEq/L to -1.6 mEq/L.





HAD immediately restored pH and BE to prehemorrhage values, by increasing pH and BE from 7.375 to 7.482, and from 0.7 to 4.6 mEq/L, respectively. Chloride levels increased from 109.1±0.08 to 128±2.4 mmoles/L with HSD but did not change with HAD. At 120 min, the two groups had similar acid-base parameters.

Conclusion: HAD resuscitation causes an immediate and prolonged restoration of buffering capacity without the inital hyperchloremic acidosis caused by HSD. The use of an HAD solution may extend the utility of hypertonic resuscitation to severely acidotic trauma patients.

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TITLE : EFFECTS OF HYPERTONIC SALINE ON CORONARY BLOOD FLOW AND MYOCARDIAL PERFORMANCE OF A BLOOD-PERFUSED ISOLATED RABBIT HEART.

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Background: While the vascular effects of hypertonic saline are well-documented, the cardiac effects remain under discussion. The potential mechanisms by which hypertonic saline could influence cardiac performance are still unclear since either a direct effect or a reflex change in autonomous nervous tone could be involved. An isolated blood-perfused rabbit heart was used in this study to the potential direct effects of increasing concentrations of sodium on the coronary blood flow and myocardial performance.

Methods. Reconstituted blood with red blood cells and modified Krebs-Henseleit buffer was oxygenated and equilibrated to achieve normal acid-base balance. After aortic canulation, coronary arteries were perfused at a constant perfusion pressure of 80 mmHg using the Langendorff technique. The speed of the coronary pump reflects the coronary blood flow (CBF). Atrial pacing maintained a constant heart rate of 100 $b.min^{-1}$. A cannulated fluid-filled balloon was inserted in the left ventricle (LV) to maintain constant left ventricular volume and to monitor the LV pressures. The balloon was inflated to obtain a LV end-diastolic pressure (LVEDP) of 10 mmHg. Maximal positive and negative LV pressure derivatives were determined and reflected myocardial contractility (dP/dt max) and relaxation (dP/dt min) respectively. After baseline measurements, blood perfusates with increasing concentrations of Na from 140 to 180 mmol/l were perfused intracoronarily. Before each hypertonic saline infusion, time was allowed to return to baseline values. Before and after each hypertonic saline infusion, arterial and venous samples were withdrawn for Na concentration measurements and blood gas analysis to derive myocardial oxygen consumption (MVO2) .

Results are shown in the table. Increasing Na concentrations induced a significant increase in CBF, dP/dt max, dP/dt min and MVO2 .

Na^+ mmol/l	142 ± 3	148 ± 1	168 ± 1	169 ± 2	181 ± 1	< 0.001
CBF ml/min	7.8 ± 1.2	11.6 ± 1.4	10.1 ± 1.6	10.8 ± 1.6	11.9 ± 1.7	< 0.001
dP/dt max $mmHg.s^{-1}$	1806 ± 166	2056 ± 145	2312 ± 209	2281 ± 183	2350 ± 220	< 0.001
dP/dt min $mmHg.s^{-1}$	1119 ± 125	1325 ± 137	1362 ± 176	1312 ± 173	1262 ± 172	< 0.01
MVO_2 ml/min/100g	4.7 ± 0.5	5.9 ± 0.7	5.6 ± 0.5	6.2 ± 0.7	6.7 ± 0.7	< 0.05

Conclusions. Sodium concentrations obtained with hypertonic saline infusion induced direct positive inotropic and lusotropic effects and coronary vasodilation. The increase in MVO2 is likely related to the improvement of myocardial performance. Hypertonic saline infusion is associated with benefecial effects on cardiac performance.

Evidence for altered expression of the L-selectin (LECAM-1) on human blood PMNs by hypertonic saline

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Ischemia followed by reperfusion is associated with the activation of leukocytes which adhere to the microvascular endothelium via specific leukocyte adhesion molecules contributing to the manifestations of reperfusion injury through formation of oxygen free radicals and release of cytotoxic enzymes. Studies from our laboratory have shown that infusion of 7.5 % saline (4 ml/kg b.w.) effectively attenuates postischemic microvascular disturbances in striated skin muscle of the hamster, presumably through reduction of endothelial swelling and leukocyte-endothelial interaction. This study was performed to investigate the effects of hypertonic saline on the expression of the leukocyte adhesion molecules CD11b/CD18 and L-selectin *in vitro*.

Polymorphonuclear leukocytes (PMNs) were separated from the blood of healthy volunteers (n=6) by dextran sedimentation and Ficoll gradient centrifugation. Isolated PMNs were then incubated for 10 minutes under hypertonic conditions (1.8%, 2.7% NaCl) at 37°C. Thereafter, monoclonal antibodies directed against the leukocyte adhesion molecules CD11b/CD18 and the L-selectin were added for 30 min at 4°C; the expression on the cell surface was assessed by flow cytometry. Controls were performed with incubation of PMNs in 0.9% NaCl.

Cell volume decreased from 100% in 0.9% NaCl to 77.4±3.6% and 62.9±4.0% after incubation with 1.8% and 2.7% NaCl, respectively. The expression of the CD11b/CD18 molecules was not altered by the administration of the hypertonic NaCl solutions, while the L-selectin was significantly reduced ($P < 0.05$) after incubation in 1.8% and 2.7% NaCl to 78.3±5.1% and 56.8±4.8% as compared to 0.9% NaCl. Resuspension of the so-treated cells to normotonic conditions prior to incubation with antibodies yielded baseline cell volumes and was still accompanied by significant reduction of L-selectin expression, indicating irreversible disappearance of this molecule on the cell surface.

These data suggest that the inhibitory effects of hypertonic saline on leukocyte/endothelial interaction elicited by ischemia-reperfusion *in vivo*, may be partly due to the decreased expression of the L-selectin on PMNs, presumably through shedding of this receptor from the cell surface.

Efficacies of hypertonic saline solution on the cardiac functions and the plasma volume during endotoxin shock using dogs.

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Background: This experiments were conducted to investigete the efficacies of 20% sodium chloride on the cardiac functions and the plasma volume expansion during endotoxin shock using dogs.
Methods and Results: 3mg/kg of LPS was injected to 10 dogs. Three hrs. later, 1.5ml/kg of 20% NaCl (HSS) was injected iv.. HSS enhanced 178% in aortic ascending blood flow (doppler method), 111% in systolic left ventricular pressure, 113% in dp/dt, 176% in CVP when compared with a 3 hrs. values after endotoxin injection. Total peripheral resistance decreased after HSS. Both serum K^+ and Ca^{++} decreased. Both pH and base excess decreased. As for the determination of the plasma volume, other ten mongrel dogs were divided into two groups of 5. Group 1 dogs were administered 0.9% saline solution (PSS) and 20% HSS for group 2. Ebans blue dye dilution methods was taken for measurement of the plasma volume. The first measurement of the plasma volume was conducted before endotoxin administration in two groups. Three hrs. later, when PSS or HSS was administered, the plasma volume was measured again. Control plasma volume revealed 715.6 ml in PSS group, 633.5 ml in HSS with out statistic significant difference. Three hrs. later the plasma volume revealed 442.3 ml in PSS group, and 447.8 ml in HSS group after PSS or HSS administration. There was no statistical significant differencein two groups.
Conclusion: An increase of aortic ascending blood flow after HSS was considered to be due to improvements of cardiac output based upon an increase of preload which was represented by an increased CVP and a decrease of afterload which was represented by a decreased TPR. Depletion of serum K^+ after HSS may be relative changes against . an increase of sodium chloride. It was considered that the depletion of serum calcium after HSS might has shifted to intracardiac muscle and this entry of calcium chloride might have enhanced the cardiac contraction.

An enhancement of systolic left ventricular pressure and Peak dp/dt after HSS reflects the strength of the cardic muscle contructure and this enhancement may be direct positive inotropic action of HSS to the cardiac muscle.

In the present experiment, We investigated whether HSS enhanced the circulating plasma volume using endotoxic shock which easily produce plasma leakage from the vessels to extravascular space. The circulating plasma volume did not produce an increase of plasma volume after HSS. From these experimental facts, we thought that the ciculating improvements after HSS might have been due to improvements of pre and afterload and direct effects to the cardiac muscle. However, We do not deny completely the osmolar effects by HSS which draw water from cells into interstitial spaces.

ISOCHLOREMIC AND ISONATREMIC FORMULATIONS FOR HYPERTONIC RESUSCITATION FROM SEVERE UNINTERRUPTED BLOOD LOSS IN DOGS.

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Background: Hypertonic saline dextran (7.5% NaCl + 6% dextran 70 - **HSD**) is effective in the treatment of a canine model of pressure driven hemorrhage, but induces a small recovery of O_2 consumption (VO_2), **in spite of a significant increase in** O_2 availability (DO_2). Previous data show that an isochloremic hypertonic solution (0.9% NaCl + 9.2% sodium acetate 6% dextran 70 - **HAD**) induces a response with lower pressure but higher cardiac output, DO_2 and VO_2 as compared to **HSD**.
Methods: This study compares the effects of 3 isochloremic solutions (**HAD**; **HLD**: 0.9% NaCl + 12.6% sodium lactate + 6% dextran 70; **HGD**: 0.9% NaCl + 5.4% sodium acetate + 20% glucose + 6% dextran 70) on pressure driven hemorrhage with an initial bleeding rate (BR_0) of 25 ml/min, performed on pentobarbital anesthetized dogs. Treatment started 30 min after bleeding and consisted of 6 ml/kg **HAD**, **HLD** or **HGD** followed by lactated Ringer's (**LR**) infusion (25 ml/min) for 60 min. **Groups of LR-alone treated and untreated CTR dogs are included.**
Results: Pre-treatment blood loss was 43 ml/kg, arterial pressure fell from 131 to 48 mm Hg, and cardiac index from 3.15 to 0.72 $l.min^{-1}.m^{-2}$. DO_2 was reduced from 518 to 124 $ml.min^{-1}.m^{-2}$, VO_2 from 128 to 78 $ml.min^{-1}m^{-2}$. After **HAD** and **HGD** arterial pressure was not increased with respect to **LR** dogs, but **HLD** caused higher pressure. Cardiac index, DO_2 and VO_2 were significantly increased by the 3 solutions with respect to **LR** or **CTR**. VO_2 improvement was better and longer lasting with **HAD** and **HGD**. Arterial pH and base excess were restored to normal by the **HAD**, **HLD** and **HGD**. **LR** alone induced a transient but significant rise of plasma Cl^-, from 122 to 141 mEq/l, but no rise was observed in the three isochloremic groups. **HAD** and **HLD** induced hypernatremia (174 mEq/l), but **HGD** did not. The average time of survival for **CTR** was 64 min, reckoned from the start of bleeding. All of the **LR**, **HAD**, **HLD** and **HGD** dogs survived throughout the experimental protocol, but the 3 isochloremic treated groups exhibited significantly better levels of cardiac index, DO_2, VO_2 and base excess throughout the post-treatment period. **HGD** treated dogs additionally were free from hypernatremia.
Conclusion: Isochloremic hypertonic formulations induce an improved response in severe, uninterrupted hemorrhage. The effects of an isochloremic isonatremic formulation are demonstrated. Isochloremic hypertonic resuscitation induces a **HI-FLOW-LOW-PRESSURE** response, which in theory is the most appropriate for uncontrolled hemorrhage.

PRESSURE DRIVEN HEMORRHAGE AS A SIMULATION OF UNCONTROLLED ARTERIAL HEMORRHAGE: AN EXPERIMENTAL STUDY IN DOGS.

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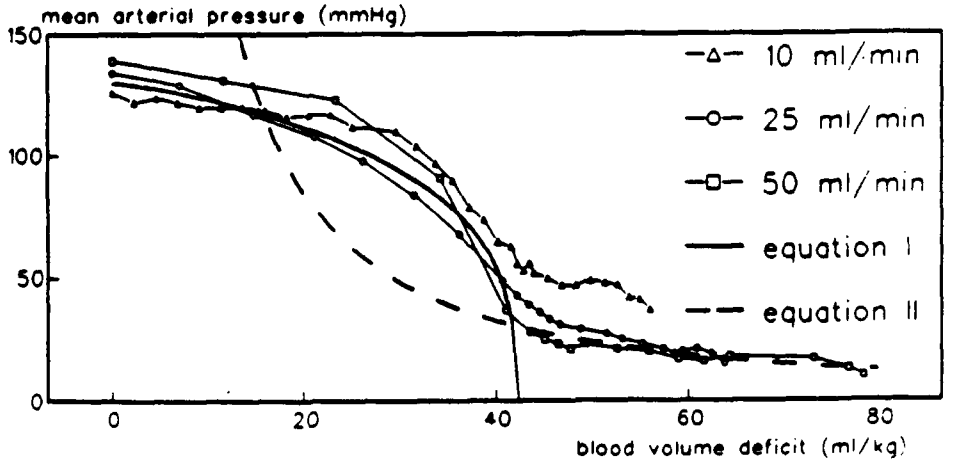
Background: Animal research on hemorrhage is more concerned with the effects of blood loss, but current emergency procedures require information on the manner of occurence of severe arterial bleeding. Pressure driven hemorrhage (**PDH**) allows the formal analysis of the course of arterial bleeding: an initial rate of blood loss (BR_0) is arbitrarily set and thereafter the bleeding rate (**BR**) is kept as a linear function of prevailing mean arterial pressure (**MAP**).
Methods: Pentobarbital anesthetized dogs were bled from a BR_0 of 10, 25 or 50 ml/min (groups: **BR10**, **BR25**, **BR50**; n = 10 per group). **BR** was adjusted to prevailing **MAP** on a min-to-min basis. Hemorrhage was performed for 150 min in the **BR10** group, and till death in the other 2 groups.
Results: All dogs in the **BR10** were alive, with an average **MAP** = 43 mm Hg after 150 min. Average survival time for **BR25** and BR50 were 69 and 41 min respectively. The course of pressure driven hemorrhage is parametrically related to BR_0 for survival time, cumulative blood loss (**CBL**), mean arterial pressure, cardiac output, DO_2 and VO_2. However, when **MAP** is expressed as a function of **CBL**, no difference occurs between groups (Fig 1). Experimental data on **MAP** as a funtion of **CBL** fit two different regressions. Initially, for a **CBL** under 40 ml/kg $MAP = 135*(1-(CBL/40)^{1.6})^{0.26}$ (I). When CBL becomes greater than **40 ml/kg** $MAP = 4000*CBL^{-1.2}$ (II).
Conclusion: **PDH** may be a useful tool for the analysis of uncontrolled arterial hemorrhage. Equation II is probably related to the ischemic response of the CNS.

Fig. 1. MAP as a function of blood loss



HYPERTONIC SALINE SOLUTION AND PULMONARY GAS EXCHANGE

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Background: Hypertonic saline solution (HTS) increases cardiac output ($\dot{Q}T$) in animals as well as in patients with hypovolemic shock. It has been shown among others by Wagner et al. (J. Appl. Physiol. 71:2191-2197,1991) that increases in $\dot{Q}T$ worsen pulmonary gas exchange due to a concomitant increase of intrapulmonary shunt ($\dot{Q}S/\dot{Q}T$). However, Constable et al. (Am. J. Vet. Res. 52:990-998,1991) showed in endotoxemic calves that HTS had no effect on $\dot{Q}S/\dot{Q}T$ and arterial P_{O_2} despite an increase in $\dot{Q}T$. The purpose of this study was to examine the effect of HTS on pulmonary gas exchange in humans with hyperdynamic septic shock.

Methods: Having obtained informed consent and approval by our ethic committee, 21 mechanically ventilated patients (F_{IO_2} 0.41 ± 0.02) with septic shock were studied. Measurements began when no further increase in $\dot{Q}T$ was noticed after adequate therapy with volume loading and catecholamines. At this point, measurements (BSL) of arterial and mixed venous blood gases, $\dot{Q}T$, mean pulmonary artery pressure (PAPM) and pulmonary capillary wedge pressure (PCWP) were taken. 4 ml/kg body weight of 7.5% saline in 6% hydroxyethyl starch were then infused over 15 min. Measurements were repeated immediately at the end of the infusion (0 min), and 30, 60 and 90 min thereafter. Data are reported as means ± SEM. Comparisons between BSL and the subsequent measurements were done by Wilcoxon test and significance (*) was accepted at 0.05.

Results: Results are summarized in the following table.

	Before HTS	After HTS			
	BSL	0 min	30 min	60 min	90 min
$\dot{Q}T$ [L/min]	7.8 ± 0.4	10.5 ± 0.5*	9.2 ± 0.4*	9.0 ± 0.5*	8.5 ± 0.4*
$\dot{Q}S/\dot{Q}T$ [%]	11.3 ± 1.7	14.2 ± 2.0*	13.2 ± 1.7*	12.8 ± 1.6*	12.6 ± 2.0*
P_{aO_2} [mm Hg]	126.8 ± 6.0	123.1 ± 6.0	113.2 ± 5.3*	119.0 ± 5.3	123.8 ± 5.3
PAPM [mm Hg]	29.4 ± 1.2	36.4 ± 1.1*	33.4 ± 1.3*	30.9 ± 1.3	30.9 ± 1.2*
PCWP [mm Hg]	14 ± 3	23 ± 1*	18 ± 1*	17 ± 1*	16 ± 1*

Conclusions: In these hyperdynamic septic shock patients $\dot{Q}T$ increased by about 35% after infusion of HTS (0 min). Despite an increase of $\dot{Q}S/\dot{Q}T$ of about 25% with rising $\dot{Q}T$ at the end of the infusion of HTS (0 min), P_{aO_2} did not change. It is possible that HTS improved the circulation in the pulmonary capillaries. This hypothesis is supported by the observation of Rocha-e-Silva et al. (Circ. Shock 19:165-175,1986) who reported an improvement of pulmonary microcirculation in patients with hemorrhagic shock treated with HTS. This improvement could have overcome the effect of increasing $\dot{Q}T$ on the $\dot{Q}S/\dot{Q}T$-$\dot{Q}T$ relationship resulting in a nearly unchanged P_{aO_2}. Of course, we cannot discern from our data between candidate mechanisms, e.g. whether this was due to an improved homogeneity of the distribution of ventilation/perfusion-ratios and/or changes in alveolar-endcapillary diffusion properties of O_2. 30 min after the completion of the HTS infusion we observed quite unexpectedly a statistically significant lower P_{aO_2} compared with the BSL value although intrapulmonary shunt did not increase. It is possible that the fall of P_{aO_2} was induced by the rise of PAPM and PCWP (0 min) leading to an extravasation of fluid into the alveolar endothelium thereby thickening the blood gas barrier and interfering with O_2-diffusion. However, the underlying mechanisms remain unclear and await further investigation.

RESUSCITATION WITH 7.5% NACL/ 6% DEXTRAN IMPROVES RENAL FUNCTION IN DEHYDRATED SHEEP FOLLOWING HEMORRHAGE

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Background: Hypertonic saline/hyperoncotic dextran (HSD: 7.5% NaCl/6% Dextran-70) is a very effective resuscitation solution following hemorrhage. However, there are concerns that treatment with HSD may impair renal function in the presence of dehydration.

Methods: Six adult ewes were chronically instrumented with indwelling vascular catheters, a Swan-Ganz catheter, and a renal blood flow probe. The bladder was catheterized on experiment days. Mean arterial pressure (MAP), glomerular filtration rate (GFR, creatinine clearance), renal blood flow (RBF), renal resistance (RR), and filtration fraction (FF, GFR/renal plasma flow) were measured: pre-dehydration, after 4 days dehydration, during the hemorrhage procedure (mean arterial pressure was reduced to 50 mmHg and held for 2 hours), for 2 hours following resuscitation with either 4 ml/kg HSD or 37 ml/kg lactated Ringer's (LR) (equal sodium load), 7 days post-hemorrhage (with shed blood returned and ewes euhydrated). This series was repeated with the alternate resuscitation treatment.

VAR	TRT	Pre-Deh	Deh	Hem	Resus	Post Hem
MAP	LR	85±3	86±3	52±1	73±2	90±4
mmHg	HSD	88±3	88±2	56±3	81±3	81±3
GFR	LR	81±3	63±8	13±5	49±10	91±9
ml/min	HSD	99±8	78±12	6±2	65±5	82±5
RBF	LR	428±64	328±64	135±32	216±42	469±86
ml/min	HSD	533±85	392±71	172±41	277±56	456±63
RR	LR	231±42	344±76	609±152	475±112	256±53
units	HSD	217±67	286±78	491±138	415±130	213±35
FF	LR	0.33±0.06	0.34±0.07	0.16±0.10	0.47±0.20	0.34±0.09
	HSD	0.34±0.13	0.33±0.07	0.06±0.01	0.44±0.20	0.30±0.06

Conclusions: Resuscitation with both treatments improved GFR more than RBF as seen by the increase in FF. HSD treatment did not cause any long-term decrement in renal function.

THE EFFECT OF THE TYPE OF COLLOID ON THE EFFICACY OF HYPERTONIC NACL COLLOID MIXTURES IN HEMORRHAGIC SHOCK DEXTRAN VS HES

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Background: Colloids increase and prolong the efficacy of hypertonic NaCl solutions in hemorrhagic shock. Two types of colloid, HES and dextran were used in previous investigations. This leads to the question of wich type of colloid should be given preference.

Methods: We compared the efficacy of dextran 60 and HES 200 000/0.5 at iso-oncotic concentrations of 6.5 or 6 % in a 7.5 % NaCl solution. 32 rabbits were bled to maintain mean arterial pressure at 35 mmHg. The 25 % shed blood volume was replaced after 40 minutes by bolus infusion either with HS-Dex (n=16) or with HS-HES (n=16). The animals were then observed for a 120-min period.

Results: In both groups immediate and complete restoration of cardiovascular function was achieved for 30 minutes and adequate restoration for 60 minutes after infusion. During the following 60 minutes signs of insufficient oxygen supply indicated the recurrence of near shock levels. Greater stability of hemodynamic efficacy was observed when dextran was added to hypertonic saline. The decrease in mean arterial pressure was lower in the dextran group ($p<0.05$). The subsequent increase in avDO2 (v.cava sup.) was approximately 50 % lower with dextran(1 ml/dl compared to 1.8 ml/dl); ($p< 0.05$). These differences occurred primarily within the initial 15 min although the differences in mean arterial pressure were recorded only after 30 - 60 min. A 50 % reduction in the decrease of lactate levels (1.1 compared to 2.0 mmol/L; $p<0.05$) in immediate response to reinfusion indicates an increased lactate absorption and thus improved perfusion of poorly perfused tissue in the dextran group. A further, possibly significant difference may be due to the different effects on the microcirculation. As evidenced by a decline in the endexpiratory arterial CO2 gradient, dextran effected a significant ($p<0.01$) improvement in decreased pulmonary CO2 elimination during shock. This indicates a greater reduction of poorly perfused, ventilated pulmonary areas.

Conclusion: In summary, in our model dextran appeared to be the superior colloid compared to HES, particularly within the first hour after initiation of treatment, although direct proof of an improved outcome has not been demonstrated.

Effect of Hypertonic-Hyperoncotic HES on Recirculation after Global Cerebral Ischemia.

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Background: Global cerebral ischemia combined with blood loss is a common feature in trauma patients. A more efficient recirculation induced by hypertonic-hyperoncotic solutions may improve clinical outcome by washout of toxic metabolites, and prevention of no-reflow. The effects of (a) 7.5%NaCl/10%HES (HHES) on cerebral reperfusion after a 15 min global ischemia plus standardized blood loss were tested in the current study as compared to (b) 10% HES (HES), and (c) reinfusion of shed blood (BLOOD).

Methods: Rabbits were anesthetized with alpha-chloralose, and artificially ventilated. After withdrawal of 10 ml/kg b.w. blood, all vessels branching from the aortic arc were occluded simultaneously for 15 min. At reperfusion the animals (n=10/group) were infused with HHES (5ml/kg), HES (10ml/kg), or BLOOD (10ml/kg), and observed for 5 hrs. Reperfusion was followed by three methods: electromagnetic flowmetry of the left carotid artery, measurement of basilary artery velocity by transcranial Doppler, and laser doppler flowmetry of the cortical microcirculation at two sites. Mean arterial blood pressure, central venous pressure, intracranial pressure, brain cortical and core temperature, jugular vein O_2-saturation, and somatosensory evoked potentials were continuously recorded. Blood gases, glucose, Na^+, K^+, Hb and Hct were determined at defined intervals.

Results: Two out of 10 rabbits died in the HES group, whereas all other animals survived 5 hrs. The postischemic hyperperfusion phase was 30-50% more pronounced for 25-30 min in the HHES group than in HES and BLOOD (basilary art. and carotid art.). The microcirculatory flow increase was maximal after 5-7 min with HHES and BLOOD, but only after 12-14 min with HES. The protracted onset of reperfusion in the HES group was also reflected in a slow recovery of the jugular vein O_2-saturation. Intracranial pressure increased in all groups to 8-9 mmHg during postischemic hyperperfusion, and, in spite of the increased cerebral perfusion, normalized (3 mmHg) within 15 min with HHES as compared to 100-120 min with HES or BLOOD (significant for 110 min).

Conclusion: The results are in favor of a beneficial role of hypertonic-hyperoncotic treatment for global cerebral ischemia: Fast reperfusion may help to wash out toxic metabolites; no-flow may be prevented by osmotic shrinkage of the capillary environment.

HYPERTONIC SALINE FOR REVERSAL OF ISCHEMIA-INDUCED CARDIAC DYSFUNCTION IN THE ISOLATED RAT HEART.

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Background: The efficacy of hypertonic saline (HS) for reversal of ischemia-induced cardiac dysfunction is still not known in detail. HS has been considered both to depress myocardial function (1) and to exert direct stimulatory effects (2). Therefore the therapeutic effects of HS on the ischemic isolated rat heart have been assessed more in detail in the present study.
Methods: The function of isolated, paced (325 beats/min) rat hearts, perfused according to the Langendorf perfusion technique at a filling pressure (LAP) of 7.5 mm Hg was assessed as follows: *Group I* : Control period for about 15 min at aortic pressure (AP) of 80 mm Hg followed by ischemia (AP 25 mm Hg for 9 min) treated at 9 and 18 min by HS administration. At 27 min AP was normalized. *Group II* : Ischemia as in group I. No HS administration. *Group III* : No reduction of aortic pressure. HS as in group I. Aortic flow (AF), coronary flow (CF), and pO2 of the venous effluent were continuously recorded. Stroke volume (SV), myocardia oxygen extraction, oxygen consumption (MVO2) and lactate production were determined.
Results: HS caused a transient reduction of AP, SV and CF, and increase of LAP in non-ischemic hearts. HS was not found to influence CF, MVO2 or lactate in ischemic hearts although SV decreased transiently at the administration.
Conclusion: HS seems to have a transient depressive effect on the non-ischemic as well as on the ischemic myocardium when given in amounts at which a sodium level of about 150-160 mmoles/L is acutely reached.

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IS A COMBINATION OF HYPERTONIC SALINE AND HYDROXYETHYL STARCH (HYPER-HES) A NEW CONCEPT IN TREATMENT OF RAISED INTRACRANIAL PRESSURE?

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Background: Beside balanced salt solutions, solutions of plasma proteins or exogenous macromolecules are used for initial volume replacement after hemorrhage or trauma. A new approach was suggested by Velasco who was successful in resuscitating dogs with small volumes of hypertonic saline. As only a few animal studies have worked on the intracranial effects in these solutions we sought to evaluate the effect of a combination of 7.5% NaCl and 6% Hydroxyethyl starch 200.000 on intracranial pressure (ICP) in patients with head trauma.

Methods: In a total of 18 polytraumatized patients with head injury epidural ICP probes were implanted. In order to treat and prevent hypovolemic states 4 ml/kg BW HYPERHES were administered when serum osmolality was below 300 mEq/l. HYPER-HES was given over a period of 15 minutes. Heart rate, MAP and ICP were recorded continuously. CPP was calculated as the difference between MAP and ICP. ETCO2 was kept within 28-32 mmHg. Patients were allocated to group I (ICP baseline values 20 mmHg, n=5) or group II (ICP baseline alues > 20 mmHg, n=13). Hemodynamic data were evaluated prior to administration as a control, and 5 and 15 minutes following HYPER-HES infusion. S-sodium and S-osmolality was determined before and after the infusion. Period of observation was 6 hours to discern a rebound phenomenon. Paired t-test was used for statistical analysis.

Results: Hemodynamic data are shown in the following table.

		Control	HYPER-HES 4 ml/kg 5 min	15 min
MAP	I	82±6	89±4	92±6*
	II	83±3	90±3*	89±3*
ICP	I	11±2	5±1	3±2*
	II	30±4	15±2*	13±2*
CPP	I	71±5	85±5*	89±7*
	II	56±4	77±4*	77±4*

S-Sodium (I: 137±2 to 145±2; II: 138±1 to 144±2; mEq/l) and S-osmolality (I: 293±4 to 310±4; II 299±4 to 314±3; mOsm/l) increased significantly in both groups.

Conclusion: As HYPER-HES decreases ICP, improves CPP and shows no rebound phenomenon, it may become an ultimate step of therapy in otherwise incurable brain swelling.

HYPERTONIC SALINE-DEXTRAN IN THE TREATMENT OF HEMORRHAGIC SHOCK: CLINICAL TRIAL IN THE EMERGENCY ROOM.

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Background: Hypertonic saline dextran (**HSD**) effectively improves hemodynamic parameters in patients with hemorrhagic shock admitted the Emergency Room (**ER**). However, no differences in outcome were observed in a previous study in which **HSD** was compared to standard isotonic treatment (Younes, RN; Surg Forum 39: 642, 1988). The present study evaluates pre-treatment prognostic factors that predict a beneficial effect of **HSD**.

Methods: Trauma patients with hypovolemic hypotension (n=200) admitted to the **ER** with hemorrhagic shock were randomized (double-blind) to receive 250 ml IV bolus of hypertonic 7.5% NaCl + 6% Dextran 70 (**HSD**, n=93), or of isotonic 0.9% NaCl (**IS**, n=107) as the 1st treatment, followed by standard resuscitation. Pretreatment factors assessed were: Sex, age, cause of hypovolemia, Trauma Score, Glasgow Index, and mean arterial pressure on admission. Both groups were compared for survival at 24 hours and at 30 days post-admission day. Infused volumes of isotonic fluid and blood/blood derivatives were registered.

Results: No significant difference in overall 30 day survival rate between **HSD** (26/93) and **IS** (35/107); twenty-four hour survival was significantly higher (p=0.04) in **HSD** patients with severe trauma (high trauma score, low Glasgow Index, and MAP < 70 mm Hg). The cause of hypovolemia was not a significant prognostic factor.

Conclusions: Thus, **HSD** is beneficial in patients with severe hypovolemic shock and trauma, resulting in a better 24 hour survival rate compared to standard isotonic saline resuscitation in the ER.

Supported in part by Laboratorios B Braun.

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